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AN ASSESSMENT OF STREPTOMYCIN IN MEDICAL PRACTICE.[1]

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IT is just five years since the isolation of streptomycin was announced by Waksman and his co-workers,[1] and this was followed by the report from the same workers that "Streptomycin was found to be highly effective against Mycobact. Tuberculosis and other organisms". Not long afterwards Feldman and Hinshaw established that streptomycin was effective in the treatment of experimental tuberculosis in guinea-pigs.

From this beginning there has evolved a broad field of valuable therapy in the use of streptomycin, a field which includes such diverse conditions as tuberculous meningitis, tularæmia and *Proteus vulgaris* infections. A writer in the *British Medical Journal* in September, 1946,[2] was moved to comment as follows: "The unwary philosopher may ask himself whether with streptomycin complementary to penicillin there will be any pathogenic bacteria for human beings to die of, in the Brave New World." Any undue optimism in this direction was stilled early by the recognition of the development of resistant strains. Karlson, Feldman and Hinshaw,[3] in 1947, showed that on contact with streptomycin, either in the test tube or in the human or animal body, *Mycobacterium tuberculosis* gives rise to resistant strains which require far greater concentrations of the drug for their inhibition or destruction. When inoculated into animals, streptomycin-resistant cultures retained their resistance and no longer responded to streptomycin therapy.

A report of 1000 cases of various infections treated by streptomycin was issued late in 1946 by the American National Research Council,[4] and a review of the treatment of 100 cases of tuberculosis of various types by Hinshaw, Feldman and Pfuetze[5] was published at the same time. These two reviews, which repay careful study, form a solid basis for our present knowledge of the scope and limitations of streptomycin therapy, although considerable modification of practice, especially with regard to dosage of the drug, has occurred lately.

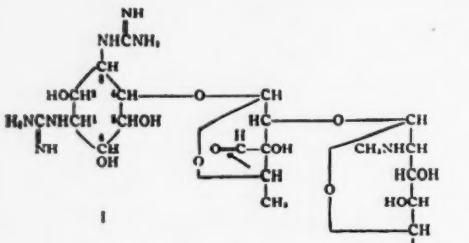
About the same time, in September, 1946, the Medical Research Council in Great Britain appointed a committee to plan and direct clinical trials with streptomycin in the treatment of tuberculosis. Because of limited supplies of the drug, the committee decided to restrict the tests at the outset to a few acute and usually fatal forms of the disease, including tuberculous meningitis in children and acute miliary tuberculosis. Later, in 1947, the investigation was extended to include patients suffering from tuberculosis of the lungs, a control group being obtained by taking half at random from a selected group of 107 patients. Results have been reviewed at quarterly meetings held at the Ministry of Health, London, at which clinical and pathological reports were presented and subjected to critical review. Several of these reports have been published in the medical Press. It is hoped in this way to avoid "the errors due to empirical evaluation of drugs in the chemotherapy of tuberculosis".

Important contributions to our knowledge were made in November, 1947, by the publication of a report from the Committee on Therapy of the American Trudeau Society, collaborating with the Veterans' Administration,[6] and issued under the chairmanship of Dr. H. C. Hinshaw, together with a comprehensive review by the Veterans' Administration.[7] The results and limitations of streptomycin therapy were fully reviewed, and attention was drawn (perhaps for the first time) to the danger to the community in the possibility that tuberculosis might be spread by streptomycin-resistant organisms.

[1] Read at a meeting of the Victorian Branch of the British Medical Association on March 2, 1949.

During this same period clinical trials with streptomycin in various infections, especially in tuberculosis, were being proceeded with on the Continent, considerable limitation being imposed by the shortage and irregularity of supplies of the drug. Notable amongst these European centres which I visited last year was the Pediatric Clinic of Florence, where, under the directorship of Professor Césare Cocchi, intensive research on the therapy of tuberculous meningitis and miliary tuberculosis with streptomycin and ancillary agents, such as "Solfone" and vitamin *A*, has yielded spectacular results.

Briefly, the salient facts about streptomycin may be summarized as follows. Streptomycin is an antibiotic agent, obtained from *Streptomyces griseus* and made available as the hydrochloride and the sulphate. It is water-soluble and basic in reaction, and the salts are relatively thermostable. It is not absorbed from the gastro-intestinal



Structure of streptomycin

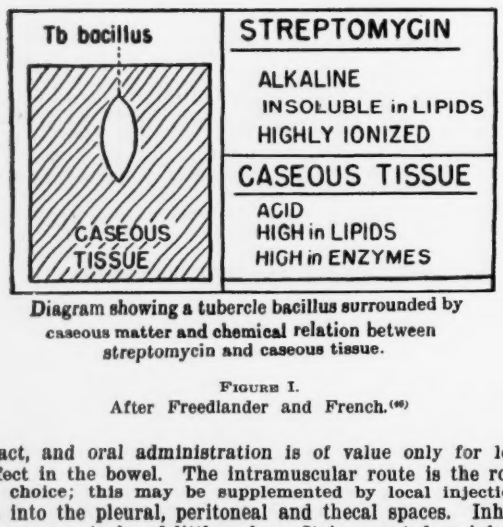


Diagram showing a tubercle bacillus surrounded by caseous matter and chemical relation between streptomycin and caseous tissue.

FIGURE I.
After Freedlander and French.[66]

tract, and oral administration is of value only for local effect in the bowel. The intramuscular route is the route of choice; this may be supplemented by local injections, as into the pleural, peritoneal and thecal spaces. Inhalation seems to be of little value. It is excreted mainly by the kidneys. The structural formula and biochemical relationship to caseous tissue are shown in Figure I.[66] Streptomycin is both bacteriolytic and bacteriostatic to tubercle bacilli. The principal effects on the bacilli are loss of acid-fastness, increase in granulation, and, in highly bacteriostatic concentrations, shortening of the rods.[66]

The field of therapy may be broadly outlined as follows.[65]

1. Streptomycin is effective in many Gram-negative bacillary infections, for example: (*a*) tularæmia; (*b*) *Hæmophilus influenzæ* infections; (*c*) urinary tract infections, wound infections and bacteriæmia due to *Bacterium coli*, *Proteus vulgaris*, *Bacillus pyocyaneus* and *Aerobacter aerogenes*; (*d*) plague; (*e*) meningitis due to all Gram-negative bacilli; (*f*) infections due to *Bacillus Friedländer*; (*g*) Shigella dysentery.

2. Streptomycin is occasionally effective in infections due to Gram-positive organisms, and to streptomycin-sensitive strains of organisms not responsive to penicillin.

3. Streptomycin is partially effective (degree of effectiveness undetermined) in (*a*) tuberculosis (see also below), (*b*) pertussis, (*c*) leprosy, (*d*) gonorrhœa.

4. Streptomycin is ineffective in these "commoner" conditions: (*a*) typhoid fever, (*b*) paratyphoid fever, (*c*) amœbic dysentery, (*d*) undulant fever, (*e*) acute rheumatic fever, (*f*) malaria, (*g*) virus infections, (*h*) mould and fungal infections, (*i*) syphilis, (*j*) Salmonella infections.

With further reference to the effectiveness of streptomycin in tuberculosis the following grouping may be made:[9] (i) tuberculous lesions in which the effect of streptomycin seems clear cut and impressive—draining cutaneous sinuses, upper respiratory ulcerations, glossitis, ileo-colitis and peritonitis; (ii) tuberculous lesions in which the therapeutic efficiency is less well defined—pulmonary, genito-urinary, orthopædic, pericardial and ophthalmological; (iii) disseminated lesions in miliary and meningeal tuberculosis, in which not only is the place of streptomycin well defined and impressive, but also it is the only known therapy of any effectiveness.

BRIEF REVIEW OF THE LITERATURE.

Tuberculosis.

Waksman[1] has made the following statement:

> Streptomycin possesses all the desirable properties as a potential chemotherapeutic agent in the treatment of tuberculosis.

Non-Surgical Pulmonary Tuberculosis.

At the end of 1947 the Veterans' Administration reported[7] that streptomycin had affected a majority of progressive or stationary exudative pulmonary lesions favourably, the effect being manifest within the first sixty to ninety days of treatment. On the other hand, the effect was rarely complete enough to be describd as a "cure", and was frequently only suppressive, in the sense that relapses occurred when therapy was stopped, or even during the later stages of prolonged therapy, whilst it was continued. It was agreed that in the treatment of exudative lesions streptomycin was a definite aid to bed rest.

In a review of 223 patients treated with streptomycin for pulmonary tuberculosis, also undertaken by the Veterans' Administration,[10] it was stated that little or no change occurred in the productive or fibrocaseous (pulmonary) lesions, but that some degree of clearing occurred in 85% of unstable, exudative lesions, which had hitherto been unchanged or progressive. It was concluded that "streptomycin can favourably affect pulmonary lesions of exudative type".

Howlett and O'Connor[11] report the results of streptomycin treatment in a small number of patients with chronic pulmonary tuberculosis. It is stated that a favourable effect was observed on chronically active and unstable indolent pulmonary tuberculosis of limited extent and severity and that a consistent and marked benefit occurred in patients with subacute and chronic disseminated nodular pulmonary tuberculosis. Cavity closure was observed in several cases.

Discussing the present status of streptomycin in tuberculosis, Pfuetze and Ashe[12] advise caution both in assessing the situation and in applying streptomycin to cases of pulmonary tuberculosis. The maximum therapeutic benefit occurs in pneumonic and early exudative lesions. In minimal pulmonary tuberculosis streptomycin therapy is seldom indicated. With the use of streptomycin the scope and frequency of surgical procedures are definitely increased.

In October, 1948, the Medical Research Council issued a report[13] on the short-term results of a controlled investigation into the effects of streptomycin in one type of pulmonary tuberculosis, the type being "acute, progressive, bilateral pulmonary tuberculosis, of presumably recent origin, bacteriologically proved, unsuitable for collapse therapy, aged 15 to 30 years".

Of 107 patients chosen, 55 were allocated to the streptomycin group and 52 to the control group at random sampling. At the end of twelve months there was an appreciable difference in the two groups. With regard to "improvement", 56% of the streptomycin group came into this category compared with 31% of the control group, whilst death had occurred in 22% of the streptomycin group against 46% of the control series. Streptomycin resistance was found to emerge during the second month of treatment, the experience of other investigators being confirmed.

Reviewing a small series of cases of acute tuberculosis of the lungs, Levine *et alii*[14] emphasize the value of streptomycin with collapse therapy and excision for patients for whom treatment of practical value appeared to be impossible. It is stated that "streptomycin should be used only when there are definite indications, for a definite purpose, and as a part of a completely formulated plan . . . used thus, it has an effectiveness and value unequalled by any other type of medicament".

Generally, the literature to the end of 1948 indicates that streptomycin has a useful, but ill-defined, place in the therapy of pulmonary tuberculosis. Its main value is in acute and subacute exudative cases, especially in relation to collapse therapy, for which it may well "clear the way". It is not commended for early, minimal lesions. It is of value in advanced cases only for the relief of symptoms and/or complications.

The special problems concerned with toxicity and streptomycin resistance, and with the important bearing these factors have on dosage, are emphasized by all authorities whose work has been examined.

Miliary and Meningeal Tuberculosis.

The grave prognosis of miliary tuberculosis and the rapid decline, with universally fatal results, of sufferers from tuberculous meningitis naturally focused attention early on the possible value of streptomycin in these conditions.

The early reports of treatment of these types of tuberculosis[4][5] indicated that life could be prolonged, if not saved, and healing was observed in tuberculous lesions even in what seemed likely to be fatal cases.[13][34] The Veterans' report, in November, 1947 (already quoted[7]) revealed that of 118 patients suffering from miliary and meningeal tuberculosis treated with streptomycin, 53 patients were still living after periods of up to six months; 20 had miliary tuberculosis, 22 meningeal tuberculosis, and 11 combined types. Streptomycin was given by the intramuscular route, in dosage of 1·8 to 4·0 grammes per day, with, in addition, intrathecal injections of 100 milligrammes (average) daily or on alternate days for those with meningitis. It was recognized that tuberculous meningitis was a complication to be feared in cases of miliary tuberculosis, even after the completion of treatment. The irritant effects of streptomycin given intrathecally were fully recognized. As early as August, 1946, Cairns *et alii*[16] stated that "the results indicate that intrathecal injection of streptomycin may be risky and may require certain special safeguards".

In December, 1947, Debré and others[17] were able to report (with perhaps Gallic exuberance) that "the tuberculous meningitis ward is like a playroom, where the liveliness provides a constantly touching scene". They give details of 118 cases of tuberculous meningitis in patients of ages varying from infancy to twenty-one years, with good result in 46—that is, nearly 40%. Some of these were treated surgically for hydrocephalus.

The report of the Medical Research Council on the streptomycin treatment of tuberculous meningitis was published in April, 1948, and reviews the results in 105 cases of tuberculous meningitis treated with streptomycin. Just one month prior to publication, the minimal survival period being seven months, the number of deaths was 71, 27 of the living being classed as of "good condition". Diagnosis was made on the usual methods of examination, with special attention to the cerebro-spinal fluid findings—pleocytosis and low sugar content were considered of special importance. Those treated with combined intrathecal and intramuscular injections did better than those receiving intramuscular injections alone. The dosage was one to two grammes intramuscularly in six-hourly doses and 0·05 to 0·1 gramme intrathecally daily or on alternate days. The irritant effect of streptomycin on the meninges was frequently manifested by pleocytosis, predominantly polynuclear. With intramuscular administration of streptomycin only, the cerebro-spinal fluid level of streptomycin was low unless or until meningitis supervened; thus a rise in the streptomycin level of the cerebro-spinal fluid was of great significance and a useful indication for intrathecal treatment. It was emphasized that "what amounts practically to a new form of the disease—chronic tuberculous meningitis—is now being observed". The fatal cases were classified as follows: no response to treatment; slow progressive deterioration with no period of improvement; progressive deterioration after short initial period of improvement or no change; relapse after a long period of improvement. Hydrocephalus was a feature of these latter groups. In most cases life was prolonged by streptomycin therapy.

A point of importance might be mentioned here: the sugar content of the cerebro-spinal fluid is upset—that is, apparently increased—by a high streptomycin level in the cerebro-spinal fluid, to the degree that 100 units of streptomycin are equivalent to 30 milligrammes *per centum* of sugar as estimated by Maclean's method.

In another article published at about the same time Cairns and others,[19] working in the Radcliffe Infirmary, Oxford, reported the treatment of tuberculous meningitis with combined intramuscular and intrathecal administration of streptomycin, to which were added as required surgical procedures aimed at local injection of streptomycin into selected parts of the intracranium, at ventricular drainage and irrigation, and at relief of obstruction in hydrocephalus. Cathie[20] emphasized the irritant effect of streptomycin when given intrathecally. His case reports show that a general rise or fall in the cerebro-spinal fluid content of protein and cells gives a rough indication of deterioration or improvement in the condition. He reports a case of miliary tuberculosis without apparent meningitis, but in which tubercle bacilli were obtained from the cerebro-spinal fluid with subsequent pleocytosis. Clinical meningitis was never manifest and the miliary process in the lungs completely cleared.

At the Pediatric Clinic in Florence, Cocchi[21] has developed a system of intensive treatment of tuberculous meningitis and miliary tuberculosis, using streptomycin by combined intramuscular and intrathecal injections, with smaller dosage, and for rather longer periods, than in English practice. The dose by the intramuscular route is one centigramme per kilogram of body weight for an adult (two centigrammes for a child, three centigrammes for an infant) in three or four doses daily for three or four months. The dose by intrathecal injection is as above in milligrammes, at first once a day for one or two months, then at intervals gradually extended until the injection is given once a week as a "maintenance" dose, for an indefinite period, until the cerebro-spinal fluid findings approximate to the normal. "Solfone" (intravenously) and vitamin *A* are also administered. In recovery the cerebro-spinal fluid changes seen are that the sugar content becomes normal first and the chlorides are "rather irregular" but generally agree; the cell, albumin and globulin contents reach normality in that order. The globulin content must be normal before cure is complete; no relapse is seen after normal cerebro-spinal fluid findings have been maintained for one month.

Surgical treatment includes drainage of the spinal and suboccipital spaces and insertion of streptomycin in these places or other areas indicated by signs of block.

Results reported are very satisfactory and it is held that the mortality rate of tuberculous meningitis has been reduced to less than 20% and that a great number of patients have been fully cured without complications or relapses. Sequelæ include hemiplegia, ataxia, third nerve paralysis and psychological states. Strangely enough, no vestibular nerve trouble was experienced.

XUM

In miliary tuberculosis the dosage of streptomycin is small (about 0·75 to 1·0 gramme per day, in three or four divided doses) and is continued for three or four months or longer, and many cures are claimed. Lumbar puncture is performed as a routine measure in all cases, and intrathecal injections of streptomycin are given once or twice a week, even if the cerebro-spinal fluid is normal.

From Laennec Hospital, Bernard and others[35] have reported the results in 78 cases of tuberculous meningitis and in 54 of miliary tuberculosis treated with streptomycin. Twenty-four patients (31%) survived for more than six months in the meningitis group; in the miliary group 27 survived out of 32 without complications, and eight out of 22 with mixed miliary and meningeal infections.

At Nortull's Hospital for Children, Stockholm, in the clinic of Dr. Wallgren, children suffering from tuberculous meningitis, with or without miliary tuberculosis, are given 0·5 gramme per day in four to six doses by the intramuscular route and 0·1 gramme per day is given by the intrathecal route for meningitis only. Here was noted the differential centrifugalization of cerebro-spinal fluid and the application of the results obtained to therapeutic measures.

A final note from the literature is quoted from American sources.[13] Investigations carried out at Herman Kieffer Hospital, Detroit, have led the group there to believe that "intrathecal injection of streptomycin has no particular value and is contraindicated because of the severe toxic manifestations which may result from this method of administration".

Briefly it may be stated that uncomplicated miliary tuberculosis responds in a spectacular manner to streptomycin therapy; the patients need to be given a long period of observation and convalescence, as some develop meningitis even after several months. The question of prophylactic intrathecal injections of streptomycin to prevent this from happening is undecided.

Chorioidal tubercles are frequently seen and their evolution may be a useful prognostic guide.[22]

Streptomycin resistance does not develop in patients treated for miliary and meningeal tuberculosis; the explanation for this phenomenon is unsatisfactory. (A few notable exceptions to this rule have been reported in the Medical Research Council report, and one by Cathie from Great Ormond Street Hospital for Children.)

Tuberculosis of Mucous Membrane.

Auerbach and Stemmerman[21] emphasize that streptomycin as an aid in the healing of tuberculosis has a much greater effect on tuberculous foci in the superficial surfaces than on foci in solid organs.

Tuberculosis of the tongue is rare. Shamaskin[30] reports three cases of tuberculous ulceration of the tongue in patients suffering from pulmonary tuberculosis. In one case complete healing occurred; in the second the oldest of several ulcers had relapsed and the others had become smaller; in the third no response to treatment was seen. Streptomycin was given by intramuscular injection and by local application. The best response was seen when the ulcers were of short duration. Claiming (incorrectly) to be reporting the first case of tuberculous ulcer of the tongue treated with streptomycin, Wolfer and others[27] reported early in 1948 a case of tuberculous ulcer of the tongue of nine months' duration. The patient was suffering from chronic pulmonary tuberculosis. The total quantity of streptomycin given was 75 grammes in three months, a dose of one gramme per day. Local application by infiltration into the ulcer was tried, but found to be ineffective. Complete healing with epithelialization was obtained. The chest condition was unaltered and the sputum continued to contain tubercle bacilli. The Veterans' Administration report[7] mentions eight cases of ulcerative tuberculous lesions of the tongue or tonsils, with healing in five and improvement in two, the streptomycin being administered by the intramuscular route.

Tuberculosis of the upper part of the respiratory tract, including the larynx, forms one of the commonest complications of pulmonary tuberculosis. As the pharynx and larynx are readily available for direct examination, changes in them can be closely observed. All observers are agreed on the profound and long-term benefits obtained by treating with streptomycin patients suffering from ulcerative lesions of the upper part of the respiratory tract. Keefer *et alii*[4] reported six cases in which the lesions were observed to heal in four to six weeks. Hinshaw[5] gave details of seven cases with prompt success in five. The Veterans' Administration reported[7] the results of treatment in 81 mixed cases and emphasized the rapidity and extent of healing in ulcerative lesions, fibrotic lesions receiving little benefit. It was found that the aerosol route was of little value, intramuscular administration being required in practically all cases. Black and Bogen,[28] reporting 34 cases of tuberculous laryngitis treated with streptomycin, stated that 13 of the lesions were healed and 17 relieved. Pain and dysphagia were relieved and recovery of the voice occurred. They remark that "streptomycin has been in our experience by far the most effective treatment so far known for tuberculous laryngitis".

Ulcerative lesions of the tracheo-bronchial tree are similarly benefited by streptomycin therapy; this section is being dealt with by Dr. J. Hayward.

With regard to tuberculosis of the intestine, in the Veterans' Administration report[7] it is recorded that "immediate results in the cases of enteritis were uniform and remarkable". Anorexia, pain and abdominal tenderness disappeared within one to two weeks of the start of treatment. Diarrhœa usually stopped within two weeks. In nine cases of tuberculous peritonitis complete relief of symptoms was obtained in eight. Streptomycin was most effective when given by the intramuscular route.

Sweany[20] reports a composite summary of 11 cases of tuberculous enteritis, with rapid symptomatic benefit from streptomycin and improvement in general condition. Evidence is ample to indicate the usefulness of streptomycin in this respect, even for palliative treatment only.

Tuberculosis of the Skin.

Keefer[4] reported three cases of skin tuberculosis of the *lupus vulgaris* type treated with streptomycin. One patient only showed temporary improvement. Hinshaw[5] reported three patients with *lupus vulgaris* and one with sarcoidosis who were treated with streptomycin; the condition of one patient with lupus was improved, the others showed no definite benefit. More recently Cornbleet[50] has reported favourably on the use in *lupus vulgaris* of streptomycin in combination with calciferol.

Other "Medical" Tuberculous Conditions.

Primary tuberculosis was mentioned in Hinshaw's report[5] in 1946, but no conclusions were arrived at. The literature available has not been informative on this matter. At Nortull's Hospital, Stockholm, the use of streptomycin was being applied last year to children with primary tuberculosis in the first year of life and in early adolescence because of the danger at these ages. Results were not available.

Pericardial tuberculosis and ophthalmic conditions of tuberculous origin "do not appear to be particularly benefited by streptomycin, but experience with these lesions is meagre".[9]

Non-Tuberculous Infections.

Only the principal non-tuberculous conditions will be mentioned.

Ophthalmological Infections.

Bellows and Farmer[30] have reviewed the literature to the date of their paper (1947) and have reported cases of ocular infections treated with streptomycin. The cases include meningococcal conjunctivitis and *Bacillus pyocyaneus* infection of the cornea. The point is made that higher concentrations can be obtained in most of the ocular tissues by local administration than by the systemic route, and systemic therapy is not necessary for purely ocular infections.

Owens[31] reported a case of corneal abscess successfully treated by local applications of streptomycin after penicillin and sulphamerazine had failed. The causative organism was *Bacterium coli*.

A case of panophthalmitis due to infection of the umbilical cord by *Proteus vulgaris* was reported by Somerville-Large;[32] 2·5 grammes of streptomycin were given over six and a half days, with a good result after evisceration. Pathological examination showed that the drug is capable of permeating the uveal tissue.

Pulmonary Infections.

Acute or chronic pulmonary infections due to organisms sensitive to streptomycin may be successfully treated by the drug. Foremost amongst these is Friedländer's bacillus infection, which responds readily. Keefer[4] reported a series of 44 patients in this group, of whom 17 were infected with Friedländer's bacillus, in some cases with other organisms added; 13 of the patients recovered. The need for early treatment was emphasized; intramuscular injection may be supplemented by aerosol therapy or even intrabronchial administration. C. Wilson,[33] in a report to the Medical Research Council on clinical trials with streptomycin in non-tuberculous infections, reviewed 14 cases of bronchiectasis and pulmonary abscess so treated, with a combination of inhalation and intramuscular injection. Results were inconclusive, as were also trials in the treatment of whooping-cough, although streptomycin has a strong bacteriostatic action against *Hæmophilus pertussis*.

Influenzal Meningitis.

A summary of 100 cases of *Hæmophilus influenzæ* meningitis by Keefer in 1946[4] showed that 66 patients were cured, 13 were improved and finally recovered, one was improved but relapsed, three showed no effect, and 17 patients died. Most of these were treated by combined intramuscular and intrathecal administration of streptomycin with other remedies then standard treatment.

Wilson[33] reported 43 cases, with recovery in 74% of 34 of the cases treated with streptomycin alone. The unsuccessful cases appear to be more severe; the principal cause of failure was the rapid development of resistance by the organism. It was recommended that treatment should be by the combined intramuscular and intrathecal routes, and that streptomycin should be supplemented by penicillin and sulphonamides right from the start. The dosage of streptomycin recommended was as follows: intramuscular, 20 milligrammes per pound of body weight in four-hourly doses; intrathecal, 50 to 100 milligrammes initial dose, then 25 to 50 milligrammes daily, continued until the cerebro-spinal fluid has been sterile for seven days.

Roscoe and Gleeson-White,[34] reporting four patients treated at Addenbrooke's Hospital with the streptomycin dosage technique first described, state that three recovered and the fourth died after developing resistance to streptomycin. These writers also stress the need for combined therapy.

Gonorrhœa.

Willcox[35] in a review of the antibiotic treatment of syphilis and gonorrhœa, pointed out that streptomycin is not very active against syphilis, but is particularly potent against gonorrhœa. Cures were reported in several cases of gonorrhœa with a single intramuscular injection of streptomycin of 0·2 to 0·6 gramme. (The statement by Fleming that "penicillin is the only drug which allows the patient to have an attack of gonorrhœa twice a week" now needs revision.) As one dose of streptomycin, if adequate, is curative, the question of streptomycin resistance does not arise. As it appears that the use of streptomycin may not mask an incubating syphilitic infection, it is probable that only a three-months post-treatment period of observation to exclude syphilis will prove necessary for patients with gonorrhœa treated with streptomycin, as compared with the six months usual after treatment with penicillin.

Streptomycin Sensitivity.

The loss of sensitivity to streptomycin and the consequent limiting value of the drug in the treatment of infections and the influence on dosage used were recognized early in the brief period under review. In 1946 Finland and others[36] showed that streptomycin resistance developed as early as twenty-four hours after treatment was started in patients with urinary infections, and the occurrence of resistance in influenzal meningitis patients is important in therapy.

In tuberculosis more than in other infections for which streptomycin is being used streptomycin sensitivity is of great importance, especially in pulmonary tuberculosis. In this condition streptomycin resistance has been detected as early as the thirty-fifth day of treatment,[7] although the usual average period is about the forty-fifth day;[18] in an occasional case the period is up to five months. The results of sensitivity tests are necessarily in-vitro findings and will depend largely on the special methods used. It is, however, generally accepted that when the bacilli develop resistance *in vitro* they will no longer respond to streptomycin therapy *in vivo*. In the development of streptomycin resistance it is not known whether such resistance to streptomycin represents adaptation in the Lamarckian sense or whether certain bacilli are naturally resistant to streptomycin and simply outgrow the suppressed sensitive organisms. Marjorie Pyle, after a detailed study of eight patients at the Mayo Clinic, concluded that the factors of genetic variation and selection may be of prime importance.[37] The degree to which resistance rises suggests that adaptation may be at work also; perhaps the two factors are involved. The important fact is that streptomycin sensitivity is lost and, as far as is known, the change in bacilli which have acquired resistance is permanent; but Wolinsky and others[49] have reported reversion from streptomycin resistance to streptomycin sensitivity of organisms in two treated patients. The relationship to clinical changes is not clearly defined. Bernstein and others[45] have pointed out that an extremely small proportion of resistant tubercle bacilli is sufficient to permit growth of artificial mixtures in the presence of streptomycin. If a correspondingly small proportion of resistant tubercle bacilli were present in a lesion under streptomycin therapy it could not be assumed that streptomycin would be totally ineffective. Crofton and Mitchison[38] have found that the sooner the resistance develops, the greater is its ultimate degree; patients in whom resistance develops later, and to a limited degree, make better progress; development of resistance is apt to be followed by an increase in the number of bacilli in the sputum. On the other hand, development of resistance is not invariably followed by clinical deterioration, as patients usually continued to improve after this change had occurred, at least for a time.

Cruickshank[47] reports from Saint Mary's Hospital, London, that the effect of interrupted dosage of streptomycin in pulmonary tuberculosis has been tried, but the development of resistance occurs with interrupted dosage just as with continuous treatment, and resistant strains still come up in the second month.

The non-development of streptomycin resistance in cases of tuberculous meningitis treated with streptomycin even for many months has already been noted; no satisfactory explanation of this phenomenon has been advanced.

The public health significance of streptomycin resistance is obvious: streptomycin-resistant organisms have lost none of their infectivity and little, if any, of their virulence, and infection so caused results in disease resistant to streptomycin from the start. This is of special importance when it is remembered that most cases of tuberculous meningitis are of human origin.

A simple method of determining streptomycin sensitivity of organisms in sputum has been developed in the laboratory of Professor K. Jensen at Copenhagen.[39f] Glass slides are cut to half by division along their length, the result being slides measuring three inches by half an inch, which fit loosely into a test tube. Sputum to be tested is emulsified in a glass mortar and thin smears are made on the narrow slides by even spreading between

slides. The specimens are dried in the air, treated with sulphuric acid (6%) for five or six minutes, washed gently with distilled water, and then placed in test tubes, which contain a suitable medium such as that of Dubos or of Youmans, to which has been added a solution of streptomycin in increasing strength, ranging from a quarter of a unit to 64 units per millilitre of solution, with at least two controls (1,000,000 units = one gramme). Tubes are incubated at 37° C. for five to ten days, stained by the Ziehl-Neelsen method and examined; the growth or absence of growth on the slides indicates sensitivity or otherwise of the organisms. A method employing the same principle, but of much greater elegance, has been evolved independently by Professor S. Rubbo and Dr. P. Woodruff in the bacteriology department of the University of Melbourne.[40]

In pulmonary tuberculosis it would appear that development of streptomycin resistance indicates the point at which streptomycin therapy is no longer of value, but improvement obtained may continue, as we have no knowledge that the defence mechanism of the body is depressed during streptomycin therapy, although this possibility has been suggested.[41]

DOSAGE.

The dosage of streptomycin, as of any other drug, is the optimum amount that is required to obtain the maximum clinical benefit, short of the production of serious complications or side effects. The limiting point, at which streptomycin resistance develops, and after which presumably the drug can be of no benefit to the recipient, is important in deciding the duration of administration.

The following table of dosage for the more important conditions is based on the prevailing practice at the main centres of research and is compiled from the current literature (Table I).

COMPLICATIONS.

The complications or side effects of streptomycin therapy are not severe in the doses used and with the purity of products now available. They can be conveniently grouped as follows:[38] (i) damage to the eighth cranial nerve: (*a*) vertigo, (*b*) tinnitus, (*c*) dizziness, blurred vision and ataxia, (*d*) deafness (very rare); (ii) sensitization reactions: (*a*) fever, headache, (*b*) skin rash—maculopapular, (*c*) eosinophilia, (*d*) joint pains; (iii) renal impairment—rare; (iv) pain and tenderness at the site of injection; (v) paræsthesia of the face.

Vertigo usually develops in the third or fourth week, but is readily compensated for, and no permanent disability is left.

Eosinophilia of mild degree is common, but apparently of no particular importance.

A maculo-papular rash may occur in the first month, but usually clears completely and treatment may be continued.

Toxic encephalopathy has been reported in a few isolated cases.[81]

Sensitivity to the drug may develop in those administering the injections, and nurses and others may develop "dermatitis" involving the hands and face after several months of its use. This has not occurred in my experience, as yet.

Recent reports on dihydrostreptomycin by Hinshaw and Feldman[44] indicate that this drug is probably of equal activity to streptomycin, but less likely to produce symptoms of vestibular dysfunction. It does not produce eosinophilia. It is more irritant locally than streptomycin.

GRESSWELL CASES.

Since streptomycin was first available in 1947, 29 patients have been treated with the drug at Gresswell Sanatorium. They were all males, of ages varying from fifteen to forty-six years, the majority being in the second and third decades of life. They were suffering from pulmonary tuberculosis, mainly in the middle or advanced stage, with acute manifestations, and some with extra-pulmonary tuberculosis, as listed below (Table IV).

Treatment.

Streptomycin was given by the intramuscular route. The dosage varied from 0·5 gramme to 2·0 grammes per day in two or three divided doses. The duration of treatment varied from two to four months, the longest period being 127 days. In the later period the dosage was 0·5 to 1·0 gramme per day in one or two injections for sixty days. All patients were on bed rest during the course of treatment and for some time subsequently, depending on their condition. Collapse therapy was applied in three cases subsequent to the course of injections.

Results.

As the majority of the patients were treated during 1948 and several have just completed treatment, the statement of results must be considered in the nature of an interim report. These are set out in Table II.

Clinical improvement was based on the combination of clinical facts, the clinician's impressions and the patient's statement. "Sputum conversion" included change from "positive" to "negative" and loss of sputum in previous "positive" cases. Generally, diminution of sputum was noticed, especially during the course of treatment. All cases except one were bacteriologically established, but streptomycin sensitivity tests were not performed. Radiological changes included clearing of infiltration and change in the size of cavities. The concurrence of desirable and undesirable changes in the radiological picture was seen in some cases and made assessment difficult. Generally, radiological changes were noticed more particularly in the first two months of treatment with streptomycin, whilst the clinical changes were more gradual.

Reduction in temperature was occasionally dramatic, but generally slow and mild in degree; many of the patients treated were afebrile or only slightly febrile and showed little change. The general result is indicated in Table III.

TABLE I.

Disease.	Amount Daily.	Frequency (Daily).	Duration of Treatment.	Total.
Tuberculosis:				
(*a*) Miliary tuberculosis	Children: 0·02 gramme per pound body weight intramuscularly. Adults: 2·0 grammes.	Four times.	90 to 180 days.	
(*b*) Tuberculous meningitis	Intramuscular: As above. Intrathecal: 0·05 to 0·1 gramme.	Four times. Once.	90 to 180 days. 60 to 90 days (discontinuous).	
(*c*) Pulmonary tuberculosis and other forms.	Intramuscular: 0·5 to 1·0 gramme.	Once or twice.	60 to 90 days.	60 grammes.
Influenzal meningitis	Intramuscular: 0·02 gramme per pound of body weight. Intrathecal: Initial, 0·05 to 0·01 gramme; regular, 0·025 to 0·05 gramme.	Six times. Once.	7 to 10 days. Until cerebro-spinal fluid sterile for seven days.	
Friedländer's bacillus pneumonia	Intramuscular: 1·5 to 2·0 grammes.	Once or twice.	5 to 10 days.	10 to 20 grammes.

Of the 22 patients who have improved, 10 have been observed for more than four months; of these, seven have maintained improvement and three have relapsed.

Case XIII.—The fatal case in the series was that of a man, aged twenty-seven years, with pulmonary and generalized tuberculosis. He was very ill from the outset and the prognosis appeared to be hopeless. He received 28 grammes of streptomycin in fourteen days, when death ensued. Post-mortem examination revealed tuberculosis of the lungs, liver, spleen and lymph glands.

Case IV.—A male Chinese, aged thirty-five years, was treated with left artificial pneumothorax, which was later abandoned because of obliterative pleuritis after empyema. He developed a number of "cold" abscesses on the body, hands and leg, a large lumbar abscess (containing pus from which tubercle bacilli were isolated), and left tuberculous epididymo-orchitis. He was given 108 grammes of streptomycin in 127 days, in doses of 0·5 and 1·0 gramme. His general condition improved rapidly and all abscesses subsided, the areas affected being normal after about eight weeks.

Table II.

Change Observed.	Number of Patients.	Number of Relapses.
Clinical improvement	22	3
"Sputum conversion"	8	3
Radiological improvement	16	4
Reduction of temperature	8	—

Left orchidectomy was performed several months after the course was completed, and the pathological examination revealed pronounced repressive and fibrotic changes. The man has remained well since, at least six months after treatment concluded.

Case VII.—A man, aged thirty-eight years, had extensive infection of the left lung, with subapical cavitation and an exudative lesion in the middle zone. He was given streptomycin, 0·25 gramme twice a day for seventy-eight days, 39 grammes in all. An X-ray examination 75 days after streptomycin treatment was commenced revealed absorption of infiltration and contraction of the cavity. The sputum was decreased, but continued to contain tubercle bacilli. The general condition was much improved, with increase in weight. The improvement has been maintained for at least two months.

Table III.

Result.	Number.
Improvement	19
Improvement, but later relapse	3
No pronounced change	6
Deterioration or death	1
Total	29

Case XX.—A young man, aged nineteen years, was suffering from pulmonary tuberculosis with tuberculosis of the larynx. On prolonged sanatorium routine some improvement was evident. Streptomycin was given for forty-nine days, 42 grammes in doses of 0·5 gramme twice a day for thirty-five days, and then once a day for fourteen days. His general condition continued to improve, with a decrease in the amount of sputum and disappearance of tubercle bacilli from it. The laryngeal symptoms were relieved promptly, and this probably aided to an appreciable degree, as dysphagia had been a troublesome feature. X-ray changes were striking and showed resolution of inflammation and contraction of the cavity. His general condition is now good.

Case XXIV.—A male patient was suffering from active tuberculosis of the lungs, which had failed to respond to routine sanatorium and collapse therapy. He was given 127 grammes of streptomycin in 127 days, in injections of 0·5 gramme and later 1·0 gramme. His general condition improved, with a decrease in the cough and sputum; but the sputum still contained tubercle bacilli. X-ray examination thirty-five days after the cessation of streptomycin injections showed extension and this was associated with recurrence of symptoms and general relapse.

Case XXVII.—A man, aged twenty-seven years, was suffering from tuberculosis of the lungs and larynx and bilateral *otitis media*; there was active infiltration in the right lung, with cavitation at the apex. Streptomycin treatment was commenced at this period and continued for fifty-eight days, in doses of 0·5 gramme, first three times a day and later twice a day. The total dosage was 72 grammes. There was considerable improvement in the condition of the larynx immediately, with improvement of voice and loss of pain. The discharge from the ears decreased and later ceased, and his hearing improved. His general condition improved and a limited degree of clearing occurred in the lungs, sufficient to allow thoracoplasty to be performed. The general condition of this man is now good, but his sputum still contains tubercle bacilli.

Extrapulmonary Tuberculous Complications.

In this series of 29 patients complications were observed as shown in Table IV.

Tuberculous ulceration of the tongue, confirmed by biopsy, was present in Case VI.

This patient was suffering from active pulmonary tuberculosis; the ulcer was on the under-surface of the tip of the tongue and, when first seen, was about a quarter to three-eighths of an inch in size, irregular in outline and shallow. Streptomycin was given over seventy-six days, in a total dosage of 45 grammes. The ulcer contracted in size in the first two weeks of treatment and is now difficult to recognize, although not completely epithelialized. No symptoms are attributable to the ulcer. Improvement has also occurred in the general and pulmonary conditions, with disappearance of tubercle bacilli from the sputum.

Table IV.

Complication.	Number of Cases.	Improvement with Streptomycin. (Number of Patients.)
Ulceration of tongue	1	1
Ulceration of larynx	13	13 improved symptomatically 6 improved anatomically
Chronic *otitis media*	2	2
Metastatic abscesses	1	1
Chronic sinus from bone disease ..	2	1

The thirteen patients with laryngeal tuberculosis include one with pharyngeal ulceration also. The effect of streptomycin on this group was universally dramatic, effective and sustained. Pain was relieved, dysphagia lost, and later recovery of the voice obtained to a varying degree. Repeated review of these patients (for which I wish to acknowledge the valuable assistance of Dr. Walter Williams) showed considerable anatomical changes in an appreciable number. In the one case of pharyngeal ulceration repression of the lesions with some healing was found. Six of the patients showed improvement of the larynx, as evidenced by subsidence of inflammation and some healing of ulceration. In one case, with a fatal termination since this paper was prepared, the larynx had healed completely and the autopsy specimen showed no trace of tuberculous change on macroscopic examination; previously, extensive ulceration of the cords had been seen. In another (Case VIII) there was actually an extension of the disease in the larynx, although symptoms of irritation, pain and dysphagia were completely relieved by streptomycin.

It would appear that streptomycin is valuable in the treatment of laryngeal tuberculosis and is usually so effective and permanent that other standard forms of treatment, such as sedatives, local applications and nerve injections, are no longer necessary.

In the two cases of chronic *otitis media* treatment with streptomycin resulted in lessening of the discharge and later complete cessation in one (Case XXVII), whilst in the other (Case XXII) the discharge was less, although hearing remained unaltered.

The metastatic abscesses were observed in the case quoted above (**Case IV**) and cleared up completely.

The sinuses from bone disease were seen in two cases.

In one (Case V) the sinus was in the chest wall and of undetermined origin. The patient was given 17 grammes of streptomycin in twenty days without any effect on the discharge from the sinus or its appearance. Treatment was interrupted by the occurrence of acute appendicitis, requiring appendicectomy, and the later development of tuberculosis of one sacro-iliac joint with abscess formation.

In the other (Case XXV) the patient had pulmonary and laryngeal tuberculosis and an ankylosed tuberculous knee joint with a draining sinus of some years' duration. He was given 29 grammes of streptomycin in fifty-eight days. The discharge from the sinus ceased early in the course of the injections and has not since recurred. He has improved generally, laryngeal symptoms have been completely relieved, and X-ray examination of the chest reveals considerable clearing.

Complications of Treatment.

Toxic effects were observed in several cases, as listed below (Table V), but were never serious, and in one only (maculo-papular rash with general erythema) was it necessary to interrupt streptomycin administration. Table V shows the toxic changes noted, their frequency and the approximate time of their appearance.

TABLE V.

Toxic Manifestation.	Number of Patients Affected.	Time (Week).
Vertigo, mild degree	4	Third.
Dizziness	1	Fifth.
"Confused state"	1	Fourth.
Blurring of vision	2	First.
Headache	2	Fourth to eighth.
Paræsthesia of face	1	First.
Maculo-papular rash	3	Second to fourth.

Eosinophilia of moderate degree (1·5% to 5%) was frequently found. In one case in which a rash required temporary cessation of therapy, eosinophilia of 6% was observed; the response to "Benadryl" administration was good, the rash clearing completely.

The absence of controls makes judgement difficult. During this period of more than twelve months the general sanatorium population of some 170 patients has provided a clinical background against which this therapy is being evaluated. It is in no sense hypercritical to remark that results just as dramatic and just as sustained have been seen among patients not treated with streptomycin, and the best of streptomycin results can be paralleled from the sanatorium records of the pre-streptomycin period.

REPORTS ON PATIENTS TREATED AT OTHER INSTITUTIONS IN VICTORIA AND SOUTH AUSTRALIA.

To obtain a more composite picture of the results of streptomycin treatment, inquiries were made at other institutions for some details of the field of therapy explored and the results obtained. I wish to acknowledge my thanks to those doctors who supplied case records, from which this brief summary is compiled.

Tuberculosis.

Miliary Tuberculosis.

Four cases were reported, with good results in all four. One other case was suspect and the result was inconclusive.

Tuberculous Meningitis.

Thirteen cases were reported. Four patients were cured, one was improved, one was moribund (at the time of the report) and seven cases ended fatally. It appeared that life was prolonged in the fatal cases. One of these cases has been reported by Dr. M. Renth, who emphasized the need for early treatment and the value of streptomycin in prolonging life and relieving symptoms.[45] The one patient improved is under the care of Dr. W. Crick at Geelong Base Hospital, and the lungs are also affected by miliary tuberculosis. Treatment with streptomycin was given for about five weeks. The development or extension (shown by X-ray examinations) of the pulmonary focus, perhaps a primary focus, whilst the patient was under streptomycin therapy, is of interest.

Pulmonary Tuberculosis.

Forty-one cases of pulmonary tuberculosis of mixed type were reported; some of the patients had ulceration of the upper part of the respiratory tract and several had (presumed) tuberculous enteritis. The general impression was that streptomycin was valuable in association with surgical therapy in the control of symptoms and of complications, and that it may be of some benefit in chronic lesions. In one case—a case of Dr. K. O'Donnell at Hamilton Base Hospital—the healing of an ischio-rectal abscess was recorded. A fatal case of subacute pulmonary tuberculosis in a child, aged seven months, who failed to respond to streptomycin therapy, was recorded by Dr. J. C. Dick from Ballarat Base Hospital. Infrequency of toxic effects attributable to streptomycin was noteworthy.

Primary Tuberculosis.

More than 20 cases of primary tuberculosis in "the young and not very robust" were reported from the Adelaide Children's Hospital, Incorporated. The dosage of streptomycin was 20 milligrammes per pound of body weight for forty to sixty days. Fairly rapid arrest and radiological reduction of all primary lesions occurred and no complications have developed in any of these cases.

Tuberculous Cervical Adenitis.

Four patients with breaking-down glands and sinus formation were treated with streptomycin at the Adelaide Children's Hospital. Two responded promptly with the drying up of sinuses; one sinus closed for three months and then reopened; in the fourth case the sinus closed after some delay.

Influenzal Meningitis.

Twenty-five cases of meningitis due to *Hæmophilus influenzæ* were reported. Treatment was by standard combined therapy. Eighteen patients recovered, six have died, and one is still under treatment. In the fatal cases all patients except one were infants, the exception being an adult, aged sixty-four years.

Virus Infections.

Three cases of acute virus infections—two cases of "virus pneumonia" and one of post-varicella encephalitis—were reported. All patients recovered.

Friedländer's Pneumonia.

Two cases of Friedländer's pneumonia were reported from the Royal Melbourne Hospital. Both patients recovered after receiving streptomycin therapy for eighteen and nineteen days respectively. Friedländer's bacilli disappeared from the sputum in each case. One patient was treated recently at the Repatriation General Hospital, Heidelberg, over a period of six months; he was suffering from extensive consolidation and cavitation. Streptomycin was given for fifty-three days, to a total of 105 grammes. The patient is now ambulatory and surgical treatment is under consideration.

Undulant Fever.

Three cases of brucellosis were reported; one patient appeared to be improved with the administration of streptomycin.

Bowel Infections.

Salmonella bowel infections have been found to respond to oral administration of streptomycin. Some 20 patients suffering from severe gastro-enteritis, no pathogen having been isolated, responded to oral streptomycin therapy after

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Further information on request

*J. Pharm. & Pharmacol., January, 1949, p.60
†Science, 16th April, 1948, p. 397.

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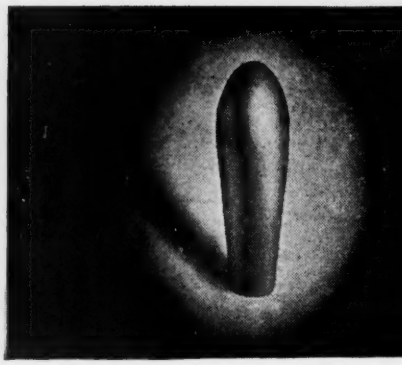

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failure of treatment with penicillin and sulphonamides. In both these clinical groups, reported from the Adelaide Children's Hospital, the dosage of streptomycin used was two grammes per day for six days, in divided doses.

Miscellaneous Group.

The remainder of the cases included various infections with streptomycin-susceptible organisms, such as *Bacterium coli*, *Bacillus pyocyaneus* and *Proteus vulgaris*, treated with uniformly good results. One patient suffering from subacute bacterial endocarditis recovered with streptomycin therapy after failure with penicillin, the infecting organism being a streptococcus.

Two patients, suffering from benign lymphocytic meningitis and agranulocytosis respectively, were treated with streptomycin, without apparent benefit.

SUMMARY.

Streptomycin is now accepted as a valuable weapon in the treatment of tuberculosis. It is the drug of choice in the treatment of generalized hæmatogenous or miliary tuberculosis, tuberculous meningitis, ulcerative tracheobronchial tuberculosis, tuberculous pharyngitis and laryngitis, tuberculous enteritis and peritonitis, and draining cutaneous sinuses. It is probably of value in genito-urinary and bone and joint tuberculosis. This statement agrees with the general conclusions reported in the current issue of the *Bulletin of the World Health Organization*.[46]

In pulmonary tuberculosis streptomycin is indicated as follows: (i) in acute pneumonic and broncho-pneumonic types; (ii) in acute exacerbations in chronic infections; (iii) in the progressive exudative type; (iv) in association with surgical treatment, including all forms of collapse therapy, on a planned régime; (v) in advanced cases, for symptomatic benefit or relief; (vi) in any stage or type of infection with which is associated advanced or progressing laryngeal or intestinal tuberculosis.

Streptomycin is not indicated (i) in early minimal lesions, (ii) in tuberculoma, (iii) in chronic fibrocavernous disease without manifest activity, (iv) in tuberculous empyema.

It may be of interest here to draw attention again to the diagram (Figure I), which indicates the nature of the barrier that may prevent streptomycin from being effective where caseation predominates, as in chronic pulmonary tuberculosis, and in caseating lymph glands before drainage. For similar reasons streptomycin is ineffective in empyemata, in which the reaction is acid, and also in lesions of the brain, which organ has a high lipid content.[46]

CONCLUSION.

I should like to conclude these remarks on a note of caution. Streptomycin has a valuable place in therapeutics, a place as yet undelimited. It cures miliary tuberculosis in most cases and tuberculous meningitis in some; it has dramatic effects in the relief of symptoms of laryngeal tuberculosis, and has been seen to be effective in the treatment of metastatic tuberculous abscesses. It is useful in other forms of tuberculosis and may alter profoundly the course of tuberculosis of the lungs. In non-tuberculous disease it is of great value, and together with the sulphonamides and penicillin helps to make a powerful antibacterial front. In tuberculosis the future of streptomycin therapy probably lies in a combination with other antituberculotics still being investigated or in the development of new compounds.

It is important that we use streptomycin intelligently, in order that resistant organisms of our own breeding may not be disseminated too widely, lest our last state be worse than our first.

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AN ASSESSMENT OF STREPTOMYCIN: SURGICAL ASPECTS.[1]

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STREPTOMYCIN is an antibiotic effective in varying degree against a wide variety of organisms, but in most cases its effect is transient. The organisms develop resistance to it in periods varying from a few days in the case of coliform bacilli to over six weeks in the case of tubercle bacilli. This time limit to its effectiveness is a most important practical consideration in the use of the drug. An infection by organisms initially sensitive, which cannot be cured within the period of its effectiveness, is liable to relapse. Unfortunately many such infections fall into this category.

[1] Read at a meeting of the Victorian Branch of the British Medical Association on March 2, 1949.

To the physician, therefore, streptomycin is often disappointing. To the surgeon, however, it is of great value, because the temporary improvement brought about by its use frequently enables necessary surgical treatment to be carried out safely and successfully on a patient who would otherwise never have been fit for the operation or would have had far less hope of a successful result from it.

Streptomycin is also of value as a prophylactic against post-operative infections. For instance, before operations on the large bowel it may be given by mouth to inhibit the bacterial flora of the colon and rectum, and before any major operation it may be given by inhalation to inhibit the flora of the respiratory tract and so help to reduce the incidence of post-operative pulmonary infections.

Finally, in certain surgical cases it may be used to relieve distressing symptoms, such as the frequency and pain associated with micturition in hopeless cases of tuberculous cystitis.

These three functions of streptomycin—as a specific therapeutic agent in combination with surgery, as a prophylactic, and as a palliative—are the main uses of the drug in surgical cases, and there is no branch of surgery in which it has not proved itself of some value. At the same time there is scarcely any operation for which it is an efficient substitute.

Any discussion of streptomycin naturally divides itself into the effect of the antibiotic on non-tuberculous diseases and on tuberculosis, and these will be considered separately.

Knowledge Necessary for the Intelligent Use of Streptomycin in Non-Tuberculous Surgical Diseases.

Streptomycin is no more effective against most strains of pyogenic cocci than penicillin, which is still the antibiotic of choice for the majority of infections with these organisms. However, of the strains resistant to penicillin, many are sensitive to streptomycin, and the latter should be used when there is bacteriological evidence that this is so.[1]

Streptomycin is effective against many Gram-negative and Gram-positive aerobic bacilli—for example, coliform bacilli, *Bacillus pyocyaneus*, *Proteus vulgaris*, diphtheroids and *Bacillus anthracis*. Since these are insensitive to penicillin and affected to a limited degree or not at all by sulphonamides, streptomycin here helps to fill a gap in our chemotherapeutic armamentarium.

In mixed infections with Gram-positive cocci and Gram-negative bacilli, streptomycin is often particularly valuable because it inhibits both groups of organisms.[2] Penicillin is usually useless in such cases, because most coliform organisms produce penicillinase, which destroys it. However, when streptomycin is given, the inhibition of the Gram-negative bacilli stops their production of penicillinase. Penicillin may therefore be usefully combined with streptomycin in the treatment of these mixed infections, because of its added effect on the cocci. The two drugs act synergically. They are also compatible and may be mixed and given in the same injection.

The range of sensitivity of organisms to streptomycin is very wide, and there is considerable variation even between different strains of any one species. For instance, many strains of coliform organisms are sensitive while others are quite insensitive to therapeutically possible concentrations of the drug. "The practical need for routine determinations of susceptibility of bacteria in conjunction with therapy is apparent."[3] Except in emergencies, streptomycin should not be given unless the laboratory has found that the organisms concerned are sensitive to it. The previous failure of other chemotherapy is not in itself an adequate indication for streptomycin.

The clostridia are insensitive to streptomycin.

In prescribing streptomycin, not only the susceptibility of the infecting organisms but also the site of the infection must be considered. Streptomycin is not diffused from the blood-stream in significant quantities into certain organs, especially the brain and the prostate, or into thick-walled chronic abscesses. It does not penetrate the pyogenic membrane so well as penicillin.[2] In fluids in serous sacs and in bile it reaches about one-quarter of the concentra-

tion in the blood serum, and in urine up to a hundred or more times the serum concentration if renal function is normal;[4] but very little of it reaches the cerebro-spinal fluid. It is absorbed but poorly from the alimentary canal, so that if ingested most of it passes out in the fæces.

The above facts determine the method of administration of streptomycin most suited to the particular infection according to its site. For instance, for septicæmia, pneumonia and urinary infection the intramuscular route is satisfactory; infections of the serous cavities are usually better managed by injections directly into them; meningitis requires intrathecal injections; granulating surfaces and chronic abscesses need topical applications; bowel infections should be treated by oral administration; and so on.

It is of little use to continue streptomycin therapy beyond the time when the organisms have developed resistance. The duration of the course should therefore seldom exceed the period taken by the organisms to become drug-fast. For Gram-negative bacilli this is usually only two or three days. For other susceptible organisms, excluding the tubercle bacillus, the time is a little longer. If the organisms disappear completely during treatment, the question of drug-fastness does not arise and treatment may cease a day or two after they have failed to appear in cultures from the lesion. Courses of streptomycin for non-tuberculous infections are therefore usually quite short.

It must be remembered that drug-fastness, once acquired, is irreversible, and drug-fast bacteria reproduce drug-fast bacteria.[1] This is true at least for considerable periods of observation. A second course of streptomycin for the same infection is therefore unlikely to be effective. One can rely on only a single short period of help by the drug. This is a most important consideration in surgical cases. The surgeon should withhold the drug until the stage in the infection at which it is judged that its help will be of most value to the patient.

It is also imperative for the surgeon to remember that streptomycin, like other chemotherapeutic agents, is scarcely ever of permanent help in infections which require surgical treatment unless the requisite surgical measures are carried out before or during the administration of the drug. The drug aids surgical treatment but seldom replaces it. Abscesses must still be properly drained, and any mechanical causes for persistence of infection, such as necrotic tissue and foreign bodies, must still be removed. In most surgical infections in which streptomycin is indicated, it is therefore best to time the streptomycin course so that it will "cover" or succeed the operation which is to be performed.

Finally, streptomycin should be used only when no other drug will serve the purpose equally well.[2] The optimum therapeutic dose is often dangerously near the critically toxic level.

These principles underlying the use of streptomycin may now be illustrated by various examples.

Some Examples of the Use of Streptomycin in Non-Tuberculous Surgical Infections.

The Urinary Tract.

Streptomycin is of value in urinary tract infections with Gram-negative bacilli, especially when combined with Gram-positive cocci; but successful therapy depends on a free flow of urine, susceptible bacteria and adequate dosage.[4][5] Abscesses must be drained, calculi removed and any other obstruction in the urinary tract relieved, or the infection will recur with the same organisms, which will then be resistant. Care must therefore be taken not to waste the evanescent effect of streptomycin when it may be more urgently needed in the same patient later, perhaps to cover a surgical procedure such as prostatectomy or nephrolithotomy.

In the treatment of paraplegics, streptomycin is unlikely to be of any permanent value in the presence of residual urine, indwelling catheters or pyelostomy or nephrostomy tubes. Its exhibition should, if possible, be delayed till tubes are removed and the patient has an automatic bladder, though one may be forced to give it before this as a last hope when there is severe upper urinary tract infection or secondary septicæmia.

In urinary infections it is generally useless to give streptomycin for more than three to five days. The recommended daily dosage is 1·5 to 2·0 grammes[6] in four-hourly intramuscular injections. It should be remembered that with poor renal function the concentration of the drug in the urine will be much less and the likelihood of toxic reactions greater. It is also important to realize that the optimum pH for streptomycin activity is 9·0.[6] The urine should always be rendered alkaline before, and kept so throughout, the course of streptomycin, except when an organism such as *Proteus vulgaris*, which flourishes much more in alkaline urine, is the main infecting agent.

The Abdomen.

It was hoped that the intramuscular administration of streptomycin would be useful for early spreading peritonitis, but as a rule it is no better than penicillin, and Pulaski[7] states that it is not so good as penicillin in localizing peritoneal suppuration. It is therefore not often indicated for general peritonitis. However, Morton and Smith[3] report satisfactory results from injecting one gramme of it daily directly into various abdominal abscesses and into the peritoneal cavity in cases of general peritonitis, but only in combination with or after adequate surgical treatment.

Reports are accumulating which indicate that streptomycin is of value in preparing the large bowel for surgical treatment. As very little ingested streptomycin is absorbed, the greater part of it reaches the large bowel, where it reduces the bacterial count of the fæces obtained by aerobic culture by 80% to 100%. The maximum effect is obtained within forty-eight hours and then it rapidly wears off, owing to the development of resistance to the drug by the fæcal organisms.

Herfort and Standard[8] recommend 0·5 gramme in water by mouth every four hours for two days before major surgical procedures on the large bowel, and suggest that if peritoneal contamination is expected, streptomycin should also be given by intramuscular injection for two days pre-operatively and two days post-operatively. Rowe and his associates[9] advise a programme which includes the administration of sulphathalidine for five to seven days and the addition of streptomycin given orally in doses of one-third of a gramme every four hours for the last two days before operation. This treatment is in addition to the routine of a low-residue diet and bowel washouts, and not instead of it.

Since streptomycin given orally reduces the blood prothrombin level, synthetic vitamin *K* must also be given parenterally.

The Chest.

Streptomycin is of doubtful value, if any, in the treatment of lung abscesses. Pulaski and White[10] report three cases, in two of which the disease was unaffected and in the other the result was inconclusive. I tried streptomycin in one case, because the patient was so ill; he was a man, aged sixty-two years, with a large, acute, putrid abscess involving the apical and subapical segments of the upper lobe of the right lung and complicating an operation for perforated peptic ulcer. There was no response to the drug, but his condition promptly improved when the abscess was drained and a huge lung slough was removed.

Empyemata due to susceptible organisms, if acute and early, may be cured by repeated aspirations and injections of streptomycin into the empyema cavity; but the majority of such lesions, as would be expected, derive little benefit from the drug until after they have been properly drained, when they usually heal rapidly without it. It is therefore not often necessary, and I have so far had no occasion to use it for empyemata.

Cohen, Taplin and Mahoney[11] have shown that the inhalation of finely powdered streptomycin is potent in reducing the flora of the naso-pharynx and bronchial tree, and have investigated its value in preventing respiratory complications after major surgical procedures. In a series of cases they found that post-operative respiratory com-

plications (bronchitis, bronchopneumonia and atelectasis) occurred in 18·7% of cases in which no antibiotic was given by inhalation, in 20% in which aerosol penicillin was used, in 2% in which micropulverized penicillin was given, and in none in which micro-pulverized streptomycin was given. The usual methods to minimize atelectasis and promote pulmonary ventilation and effective coughing were used in conjunction with the inhalation chemotherapy. The doses of streptomycin were 0·3 gramme the night before, 0·2 gramme on the morning of operation, and 0·2 gramme per day for two days after operation. After this, in one-quarter of the cases culture from the sputum or from naso-pharyngeal material gave no growth.

It would seem that when major surgical procedures have to be performed on patients who are "poor risks" because of respiratory disease, such as bronchitis and emphysema, prophylactic inhalation chemotherapy with streptomycin should be considered. An apparatus for finely powdering the antibiotic and for giving it by inhalation in this form is described and pictured by Taplin and Bryan,[12] but not in much detail.

The Soft Tissues.

The chief field of usefulness of streptomycin in soft-tissue infections by susceptible organisms is in acute infections complicated by cellulitis.[3] A course of intramuscular injections may result in resolution of such an infection. But if necrotic tissue is present, it must be removed and abscesses must be drained, and when this is done most of such infections will heal promptly without the drug. However, in the treatment of deep abscesses with mixed infections, streptomycin may help when injected daily into the abscess cavity after it has been drained. Intramuscular administration is not so useful at this stage, because the streptomycin penetrates the pyogenic membrane so poorly.

The local application of streptomycin to granulating surfaces is very valuable for removing organisms such as the coliform bacilli and *Bacillus pyocyaneus* preparatory to skin grafting.

For general prophylaxis of wound infection after civilian or war injuries streptomycin is no better than penicillin, which should still be used for this purpose.

Knowledge Necessary for the Intelligent Use of Streptomycin in the Surgery of Tuberculosis.

The principles underlying the use of streptomycin in the surgery of tuberculosis are comparable in every way with those already outlined for its use in the surgery of non-tuberculous infections. In tuberculosis the susceptibility of the strain of the tubercle bacillus in the lesions must be the subject of the same investigation before treatment, the site of the infection has the same bearing on the choice of the best routes for administration of the streptomycin, the development of drug-fastness is similarly a limiting factor, and the antibiotic is likewise of greatest value as an adjunct to surgery and is not a substitute for surgery.

The differences in the use of streptomycin for tuberculosis are related to the longer time taken by tubercle bacilli to become resistant to the drug, and to the slower evolution and healing of tuberculous lesions.

The minimum time in which tubercle bacilli may become streptomycin-fast is generally agreed to be about six weeks, and a greater and greater proportion of the organisms become resistant, the longer the period of administration of the drug is continued beyond this time. There is no unanimity in the literature as to the optimum duration of a course of streptomycin for surgical tuberculous patients, but we have come to the conclusion that in our thoracic cases very little benefit comes from prolonging it beyond sixty days. For about a year this has been the length of our routine course. This is in contrast to non-tuberculous infections, in which, as we have seen, a full course may be as short as three days.

Unfortunately tuberculous disease takes much longer to heal than sixty days. There is therefore no hope of eradicating tuberculous infection by streptomycin, as is possible with some non-tuberculous infections. Moreover, streptomycin can reach only acute exudative lesions in adequate concentrations, because only these have enough blood supply.[13] Therefore the most it can achieve is reduction in toxicity, temporary cessation of spread, and perhaps commencement of resolution of exudative lesions, relapse being common after the drug ceases to be effective. In the medical treatment of tuberculosis streptomycin is consequently often disappointing.

However, from the surgical point of view, the temporary arrest produced by streptomycin is most valuable. Post-operative spread of the disease and tuberculous infection of the wound are the complications most feared in major surgical procedures for tuberculosis. These complications have proved much less frequent when the operations are carried out with the help of streptomycin. The greatest safety seems to be afforded when they are carried out during the sixty-day period of the drug's effectiveness.

After the successful completion of the surgical programme under the protective cover of streptomycin, subsequent relapse, at least in the next few months, has been found uncommon. Few later results are yet available. This is in contrast to the frequency of relapse after streptomycin therapy without surgery. The explanation of the difference is presumably that the removal or control of the main lesions by adequate surgery usually leaves the remainder of the disease not too extensive for the resistance of the patient, aided by the usual post-operative treatment, to arrest it.

The main field of usefulness of streptomycin in the surgery of tuberculosis is, therefore, as a cover for operations, particularly for risky types of operation and for operations on "poor risk" patients. Streptomycin also may make it safe to proceed with surgical treatment at an earlier, more acute phase of the disease than has hitherto been possible.

There is as yet no general agreement on the optimum daily dosage of streptomycin in tuberculous infections. Since the discovery of the drug the intramuscular dose recommended has fallen from 3·0 grammes to 0·5 gramme per day. Since the middle of 1948 we have as a routine measure used 0·5 gramme per day in two twelve-hourly doses of 0·25 gramme in our thoracic cases and have seen no less benefit from this than from the previous larger doses. Our routine course is thus 30 grammes given in sixty days. In some clinics the 0·5 gramme is now given in a single daily dose. It is probable that the same course would be equally satisfactory for surgical tuberculous conditions outside the chest, though most reports of such cases in the literature describe larger doses.

It is strange that it should have been found that such small doses at such comparatively long intervals are just as effective in most forms of tuberculosis. Apparently in this disease it is not necessary to keep the blood level of the drug continuously above what would be an effective concentration *in vitro*. This is most fortunate, because larger doses over the long periods necessary in tuberculosis frequently have serious toxic effects, which are rare with the dose of 0·5 gramme per day.

The contrast with non-tuberculous infections is again apparent. In them the dose is usually one to three grammes a day, given in much more frequent injections, usually every four hours. The aim here is, if possible, to eradicate the infection by a "knock-out" blow—a goal which we have seen to be unattainable with streptomycin in tuberculosis. Non-tuberculous patients are usually saved by the shortness of the course from toxic manifestations due to the larger dosage.

Some Examples of the Use of Streptomycin in the Surgery of Tuberculosis.

Pulmonary Tuberculosis.

It is generally agreed that the use of streptomycin to cover pulmonary resections for tuberculosis is mandatory.[14] Moore, Murphy and Elrod[15] compared the results before and after streptomycin. Their figures are set out in Table I, together with those for the total of 24 resections, comprising 17 pneumonectomies and seven lobectomies, which I performed with streptomycin cover

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between May, 1947, and November, 1948. The evidence of these figures is incontrovertible.

Harken and his colleagues[18] state that segmental resections for pulmonary tuberculosis are relatively safe with streptomycin and advise the conservation of as much pulmonary tissue as possible, even when it contains small lesions. Two of my lobectomies for tuberculosis have been segmental. One was a removal of the lingula, performed with streptomycin and included in the above series; the other was a removal of the apical part of the lower lobe of the left lung, performed in 1946, before streptomycin was available. Both patients did well and have been back at full work for six months and two years respectively.

TABLE I.

Results of Resection for Pulmonary Tuberculosis.

Author.	Mortality Rate.	Post-operative Empyema.	Post-operative Pulmonary Spread.	Sputum Conversion.
Moore, Murphy and Elrod:				
Without streptomycin cover	26%	20%	26%	50%
With streptomycin cover	5%	6%	1·6%	90%
Hayward:				
With streptomycin cover	1 out of 24	2 out of 24	3 out of 24	20 out of 22[1]

[1] Two patients who underwent lobectomy for tuberculomata had sputum free from tubercle bacilli before as well as after operation.

The evidence for the value of streptomycin to cover thoracoplasty for pulmonary tuberculosis is less convincing. Murphy[14] last year reported that post-operative spread or reactivation was reduced from 5·6% to 2% and wound infection from 2·4% to 1·1% with streptomycin, but later in the year, with Walkup and Cheek,[17] in a series of 49 cases with 50 controls, he reports no significant difference. Because the results of thoracoplasty in suitable cases are so good without streptomycin, present practice is not to give the drug in these suitable cases unless and until post-operative complications arise. The argument that the thoracoplasty may fail and the streptomycin be necessary for a subsequent resection is also given in support of this practice.

I have used streptomycin after thoracoplasty for post-operative spread or reactivation of the disease in nine patients. In all the spread was arrested and no patient has died. Six have done well, but three are permanently the worse for the complication.

The greatest value of streptomycin in thoracoplasty is that it makes this operation possible in hitherto unsuitable cases. Harken with others[18] reports a small series of such patients and concludes that streptomycin "extends a reasonable opportunity for therapeutic success in the desperate risk patient". I first attempted thoracoplasties with streptomycin cover on patients previously considered too unstable for the operation in July, 1948, and up to November I had used the method in 16 such cases; 13 of these patients were "slipping chronics" and the other three had fairly acute exudative disease. In all the disease was extensive and bilateral. Only two of the 16 had such complications as post-operative spread or reactivation of the disease. None of them died and 12 have done well without any complications. The period of follow-up is only four to nine months; but the immediate results are surprisingly good when it is remembered that without streptomycin no surgical treatment would have been considered possible and that all these patients were otherwise doomed to a short life of chronic invalidism with "open" pulmonary tuberculosis.

In two cases I have performed a thoracoplasty several months after the completion of a course of streptomycin to arrest acute spread. Both patients have done well, but more recent experience suggests that equally good results would have been obtained in a much shorter time had the thoracoplasties been carried out during the streptomycin courses. I have never seen streptomycin make unnecessary a thoracoplasty which was otherwise indicated and it seems unwise to waste time waiting in this vain hope.

In four cases I used streptomycin to cover a cavernostomy, with satisfactory results, which gave the impression that the drug helped. Decortication of the tuberculous lung[19][20] and extrapleural pneumothorax in cases of acute exudative disease in the lung[21] have been reported free of complications with streptomycin, which also improved the results obtained with unroofing of residual tuberculous empyema cavities after thoracoplasty.

It thus appears that there is no major operation for pulmonary tuberculosis which may not be made safer by the use of streptomycin cover.

Because surgical treatment is safest during the sixty-day period of the course and because there is no guarantee in the present state of our knowledge that subsequent courses of streptomycin will be effective, it is considered wise to withhold the drug from a patient who will obviously need surgical treatment at some time until the full plan of treatment, including definite dates for his operations, has been worked out. Then the date for the commencement of the streptomycin injections is fitted into this plan. They are usually timed to begin about fourteen days before the first operation and are continued for the usual sixty days at 0·5 gramme a day.

Chest physicians as well as chest surgeons must be fully aware of the danger that premature streptomycin treatment of pulmonary tuberculosis, which may need surgical measures at a later date, may deprive the patient of the value of this drug when he most needs it as a cover for his operations. The decision when to prescribe streptomycin for pulmonary tuberculosis is therefore a grave responsibility, not to be taken lightly or without careful consideration of all possible eventualities. It will not become easier until we know more about drug-fastness in tubercle bacilli. There is "as yet insufficient evidence to make any statement regarding the return of sensitivity or the duration of resistance" of tubercle bacilli to streptomycin.[13]

The situation has been made more confusing for us because, contrary to what one would expect from the literature, our laboratory at the Repatriation General Hospital, Heidelberg, has not found streptomycin resistance in a single one of the strains of tubercle bacilli obtained from our patients after our routine 30-gramme course of the drug. Moreover, in five of the 24 resections reported in this paper the operation had to be performed under cover of a second course of streptomycin, because in each case a course had been given two or three months previously for tuberculous bronchitis. These five patients did well, but it is, of course, impossible to know whether the second courses really contributed to the good results.

Until the position is clarified by further research it is considered best in the treatment of patients who will need surgical measures, to continue whenever possible to delay the use of the drug until it will coincide with their operations.

Tuberculous Tracheobronchitis.

Streptomycin produces dramatically rapid relief of tuberculous lesions of the trachea and larger bronchi. Within a few weeks complete healing is usually seen through the bronchoscope. But where there has been considerable destruction of tissue the lesions heal by fibrosis, which may produce permanent bronchial strictures necessitating pulmonary resection. Moreover, the bronchial disease, especially when related to a peribronchial caseous gland, frequently relapses within two or three months of the cessation of the course of streptomycin. In such cases resection of the lobe or lung supplied by the affected bronchus may also be necessary.

The streptomycin may be given by inhalation for tracheobronchial disease, but we have found the usual course of intramuscular injections more satisfactory.

Tuberculous Abscesses and Sinuses.

Streptomycin has made feasible a bold attack on tuberculous abscesses instead of the usual procrastination and often inefficient aspiration.

Winterhof and Weber[32] advocate open drainage of tuberculous abscesses and sinuses under streptomycin cover. The operation should include the removal of all necrotic debris and as far as possible the excision of all tuberculous granulation tissue. For conditions such as psoas abscesses, which extend so deeply that they cannot be widely opened, these workers advise in addition daily irrigation through a long catheter, followed by the instillation of penicillin and streptomycin through the catheter.

When the abscess or sinus comes from tuberculous bone, joint, epididymis or lymph glands, the diseased tissue should whenever possible be excised at the drainage operation. If the seat of the disease is not removed, streptomycin is likely to fail either to close the sinus or, if it does close it, to keep it from reopening.

Harken and his colleagues[23] have shown that secondary closure seven to ten days after such drainage operations is often possible with streptomycin cover and frequently results in rapid healing.

Orthopædic Tuberculosis.

Jansey and his colleagues[24] found that streptomycin relieved pain in orthopædic tuberculosis and improved the patient's general condition, appetite and sleep. Caries and osteomalacia did not increase during the course, and in some cases the drug restored or preserved joint function. These workers are not very explicit about what happens after the course. Bickel and his colleagues[25] found that of 16 patients with tuberculous bone and joint disease treated with streptomycin, nine showed a good response, one a fair response and four no response, and two were too recently treated for the results to be evaluated. These workers, too, performed no operations during the course, though they did follow it with operation in some cases.

There is one type of patient who may respond dramatically to streptomycin. It is the patient with multiple scattered lesions, perhaps in half a dozen different bones and joints and in other organs as well, who is treated at an early stage, shortly after the metastatic dissemination which produced the lesions. I have seen two such patients. Nevertheless the general impression gained from the literature is that streptomycin is of limited value in the treatment of tuberculous bones and joints.

One is tempted to ask whether orthopædic surgeons have lagged behind thoracic surgeons in getting the best value out of streptomycin. Argument by analogy is notoriously dangerous; but experience in dealing with the chest makes one wonder whether there are cases of bone and joint tuberculosis in which bold and early open operation under streptomycin cover would be safe and successful and save months or even years of pre-operative immobilization.

Tuberculosis of the Renal Tract.

The prognosis of renal tuberculosis is very bad. Lloyd and his colleagues[26] state that nephrectomy in unilateral renal tuberculosis results in cure in only 50% to 55% of cases, and failure to remove the kidney nearly always leads to death within five years. They think that streptomycin will improve the outlook in these cases. They advise streptomycin alone only for the patients with very early lesions, who have a normal pyelogram and a low leucocyte count in the urine from the affected kidney. All patients with unilateral renal tuberculosis and positive pyelographic findings should have nephrectomy with streptomycin cover. The streptomycin hastens healing of the bladder and heals wound disruption and loin fistulæ. When the ureter fails to heal, streptomycin renders secondary ureterectomy safer.

Streptomycin gives temporary relief of distressing frequency of micturition and strangury in the terminal stages of hopeless bilateral renal tuberculosis; such patients should never be denied this palliative to their misery. A short two or three weeks' course is adequate, and repeated small courses may be given for recurrence of the symptoms.

Conclusion.

Though much information has accumulated about the range of its usefulness and its limitations, a true assessment of the value of streptomycin is still far from possible. However, some idea of its value is given by asking oneself the question whether one would like to be without it again. The answer is definitely in the negative, and there is no doubt that only a drug more effective against the same organisms will supplant it.

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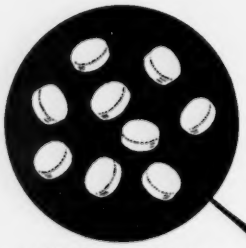

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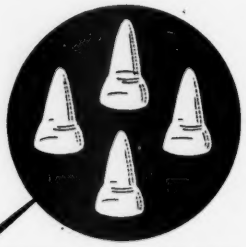

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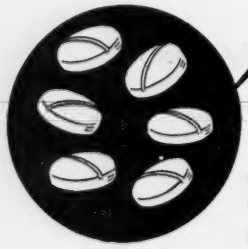

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THE TREATMENT OF ANÆMIA.[1]

By R. JEREMY,
Sydney.

General Principles of Treatment.

WHENEVER possible the diagnosis of anæmia should precede treatment. Treatment should then be given with the hæmatinic substance apparently deficient. If the diagnosis is in doubt, clinical trial of hæmatinics should be made in steps, and combined preparations are best avoided.

Response to treatment should be gauged if possible by reticulocyte counts at appropriate times and by red cell counts and hæmoglobin estimations.

A full and varied diet should be given, and it should contain a full amount of first-class protein and vitamins; the latter are probably best in their natural state. Infections should be treated if possible.

Iron Deficiency Anæmias.

Iron deficiency anæmias are characteristically hypochromic and microcytic; they may be normocytic and hypochromic. Typical examples are the idiopathic hypochromic anæmia of middle-aged women and the anæmia of chronic hæmorrhage. The presence of bleeding gastro-intestinal lesions should always be suspected, particularly in men. Any hæmorrhage discovered should be stopped if possible and iron given in large doses. The commonly used preparations are: (i) ferrous sulphate in a dosage of 9 to 18 grains per day, (ii) ferrous carbonate, 15 to 45 grains per day, and (iii) iron and ammonium citrate, 90 to 120 grains per day. Many preparations are now available, and at a reasonable cost, which contain as well as iron, copper, manganese, cobalt and sometimes vitamins. These additions are probably unnecessary, as the trace elements are usually present as impurities in the iron preparation. It is of interest that cobalt anæmia in sheep in Western Australia was first cured by the use of large doses of an iron preparation; it was subsequently found that the effective substance was cobalt, which was present in small amounts in the iron preparation.[1] Intolerance to iron in the form of dyspepsia, constipation or diarrhœa is not uncommon and it may prove to be a real difficulty. Iron should be given immediately after meals and in small doses at first; when only small doses can be taken the use of dilute hydrochloric acid as well is probably advisable. When large doses of iron are satisfactorily ingested, the use of hydrochloric acid is unnecessary. The parenteral use of iron is undoubtedly effective, but toxic reactions prevent its use in adequate dosage for clinical work. Investigators have shown that good reticulocyte responses and blood regeneration have followed its use in suitable anæmias; in one study it was found that 72% to 99% of the injected iron was apparently used for the synthesis of hæmoglobin.[2] Iron may be provided by blood transfusion; 500 millilitres of blood should provide about 250 milligrammes of iron, and this iron eventually enters the pool of body iron when the donor's red cells are destroyed. However, the transfusion of blood is not to be lightly undertaken, especially in the treatment of mild anæmia.

A non-toxic and effective preparation of iron for parenteral use would be of real value to the clinician.

Protein may be necessary for adequate blood regeneration in hypochromic anæmias. In some patients a small maintenance dose of iron may be required.

True Pernicious Anæmia.

After his first ten years' experience with liver therapy Minot made the following statement:

> The grave error in treatment is to prescribe too little liver extract or potent substitute. When there is doubt, more, rather than less, should be given. It is essential that the individual receive into his body indefinitely and with regularity, enough potent material for his given case.

[1] Read at a meeting of the New South Wales Branch of the British Medical Association on November 25, 1948.

Treatment cannot be standardized, although a dosage effective on the average can be used as a basis for treatment. While adequate oral therapy with liver, liver extract or desiccated hog's stomach remains effective, it has been largely replaced by parenteral intramuscular therapy. Parenteral therapy brings the patient regularly to the doctor, which is an important advantage, as the treatment can be supervised and it is less often neglected by the patient. There is a good deal of evidence against the proposition that crude extracts are more effective than refined extracts, even in the presence of complications in the nervous system, such as subacute combined degeneration of the spinal cord. The goal in treatment is the restoration of health, the return of the blood picture to normal and the prevention of complications in the nervous system or their relief if they are already present.

Even in severe anæmia blood transfusion is seldom required. It may perhaps be used if the patient remains dyspnœic at rest in bed, but it carries a risk of producing acute pulmonary œdema.

Initially liver extract is given intensively, and if the preparation is labelled in units, 15 units may be given each day for a week, then 15 units two or three times a week until there is a full hæmatological response and symptomatic improvement, then 15 units every two, three or four weeks for maintenance therapy. Injections at shorter intervals may lessen the liability to development of sensitivity to the extract. If the preparation is not labelled in units, then the dosage recommended by a reliable manufacturer may be accepted as a basis for treatment. It is the response of the individual patient and not the amount given in units or millilitres which determines dosage. The erythrocyte count should be maintained as near as possible to 5,000,000 cells per cubic millimetre; but it is difficult to know the patient's normal level. If the red cell count remains below 4,000,000 per cubic millimetre, or if glossitis or neurological lesions appear or recur, then treatment needs to be intensive. Response may be inhibited by the presence of an infection—for example, pyelonephritis; arteriosclerosis is often said to have an adverse effect. However, most elderly patients, presumably with degenerate arteries, respond to treatment in a reasonable manner. A fall in the mean corpuscular hæmoglobin concentration may call for the use of iron. Dilute hydrochloric acid may be used if dyspepsia or diarrhœa persists. Progress blood counts may first be made every one, two or three months; later on, when the patient's requirements are better known, they may be spaced at longer intervals.

Sensitivity to liver extract may develop, especially in women. This may occur after three or four injections or it may not occur for months. Soon after an injection there may occur flushing of the skin and injected conjunctivæ; the tongue, face and lips may swell; angioneurotic œdema and an asthmatic wheeze may be present. These reactions may be delayed an hour or so, but the patient's description should be acceptable for diagnosis. Adrenaline solution for injection should always be available. This sensitivity is probably a species and not an organ sensitivity.[3] It may be met with by changing the extract used—for example, from a pork to a beef extract. However, sensitivity to a second extract may be acquired, and then desensitization by frequent small injections may be tried, starting at 0·05 or 0·1 millilitre and increasing gradually to 1·0 millilitre. Subsequently the maintenance doses may be given more frequently than usual. Oral treatment may be necessary, and here desiccated hog's stomach can be used, or a potent liver extract for oral use, or proteolysed liver.

Folic Acid in Pernicious Anæmia.

The oral use of folic acid (pteroyl-glutamic acid) has an adequate effect on the anæmia. There seems to be some disagreement in the literature as to the completeness of this effect; reticulocytosis may be submaximal and the blood levels may not be fully restored or maintained. However, there is no disagreement that it is usually ineffective in the treatment of neurological complications; it seems clear also that these disabling and dangerous complications may be induced by its use. Wilkinson[4]

found it to bring on acute cord symptoms within fourteen days. Of 20 patients treated by him with folic acid, 15 developed symptoms of involvement of the cord.

Bethell and Sturgis[5] have reviewed their results of therapy in pernicious anæmia in relation to changes in the nervous system over a ten-year period. Whether their patients had been treated with preparations of stomach or liver for oral administration, or with crude or refined liver extracts for parenteral use, significant improvement in the neurological manifestations was shown. The improvement was limited to the first year of therapy. Bethell and Sturgis also found that mild neurological relapses due to neglect of treatment did not prevent a second improvement with effective therapy; there is a better outlook for improvement when the neurological involvement has been of short duration. These authors have found that some patients have had relief of neurological complications while receiving folic acid.

Stone and Spies[6] have found that the severe "fiery-red" mucous membrane lesions in macrocytic anæmia are found only in patients with gastric achlorhydria and achylia, and in their experience these lesions have occurred only in patients who had subacute combined degeneration of the cord. They conclude that there is a close clinical association between the gastric defect, the severe mucous membrane lesions and the degeneration of the posterior and lateral columns of the spinal cord. Folic acid is ineffective in the treatment of these patients, but liver extract and vitamin B_{12} are effective.

Patients with no anæmia, who have the neurological signs of subacute combined degeneration, and who have histamine-fast achlorhydria, should be treated intensively with a potent liver extract.

Vitamin B_{12}.

In the United States of America, Shorb found that the *Lactobacillus lactis* Dorner required a growth factor present in commercial liver extracts. Rickes isolated from liver a substance crystallizing as small red needles and called it vitamin B_{12}. It is active in pernicious anæmia in doses as small as three microgrammes; it has been shown to be effective also in nutritional macrocytic anæmia and in tropical sprue. A recent clinical report suggests that vitamin B_{12} is not responsible for sensitivity reactions to liver extracts.[7]

In England, E. Lester Smith[8] also isolated a substance from liver which appears to be identical with vitamin B_{12}. C. C. Ungley has shown this substance to be effective in the treatment of pernicious anæmia and in subacute combined degeneration of the cord. In a patient with megaloblastic anæmia of pregnancy the substance was ineffective, although the patient subsequently responded to 2·5 milligrammes of folic acid daily.

Vitamin B_{12} is a cobalt complex,[9] and its red colour appears to be at least in part associated with its cobalt complex character. Since this discovery cobalt salts have been given to patients with pernicious anæmia, but without effect. The effective action of vitamin B_{12} is proof that pernicious anæmia will respond to a single factor and does not require a multiplicity of factors. The crude substance is apparently not more effective than the refined.

Macrocytic Anæmias other than Pernicious Anæmia.

Two other forms of macrocytic anæmia may be recognized, as follows: (i) macrocytic anæmia associated with megaloblastic erythropoiesis in the bone marrow: (*a*) nutritional macrocytic anæmia, (*b*) severe anæmia of pregnancy, (*c*) the sprue syndrome—tropical sprue and idiopathic steatorrhœa, and (*d*) idiopathic megaloblastic anæmia; (ii) macrocytic anæmia associated with normoblastic erythropoiesis in the bone marrow. Such anæmia may occur after acute blood loss, with disturbance of liver function, acute hæmolytic anæmia, scurvy, myxœdema, steatorrhœa and refractory anæmia due to toxic factors; it may occur in leuchæmia (Whitby[10]).

Although the bone-marrow findings in the first group may be identical with those in classical pernicious anæmia, free hydrochloric acid may be present in the stomach, involvement of the nervous system seldom occurs and the patient may be found in a lower age group.

Nutritional Macrocytic Anæmia.

Nutritional macrocytic anæmia is commonly found in tropical regions. It was described first by Wills and her colleagues, and its frequent association with pregnancy was noted; this anæmia responded to crude liver extract and to "Marmite", but not as a rule to purified liver extract. More recent studies have shown that clinical and hæmatological improvement follows the use of folic acid. As pellagra is occasionally seen in the temperate zones in Australia, it is likely that patients will be found with nutritional macrocytic anæmia.

Severe Anæmia of Pregnancy.

The majority of the anæmias found during pregnancy are due to iron deficiency, and often this deficiency is present before the pregnancy. The prophylactic use of iron is well established and iron is usually effective in treatment; a high protein intake is important. True pernicious anæmia is seldom complicated by pregnancy, but a megaloblastic anæmia may occur, somewhat uncommonly, and this anæmia may be refractory to the parenteral administration of liver extract. Proteolysed liver and folic acid may be effective. Free hydrochloric acid may be present in the gastric juice, and investigation of the peripheral blood may show a normocytic picture. Treatment may be discontinued after cure, but the anæmia may recur in subsequent pregnancies. It would seem that there are other, as yet unclassified, anæmias associated with pregnancy, which do not respond to the usual measures, but which require blood transfusion as the only effective form of therapy. This should not be used, however, until all other measures have been unsuccessful, or unless the anæmia is severe and unlikely to respond before term.

The Sprue Syndrome: Tropical Sprue, Idiopathic Steatorrhœa.

Folic acid usually relieves the intestinal symptoms promptly, in doses of five to ten milligrammes daily by mouth. If the accompanying anæmia is associated with megaloblastic transformation of the bone marrow, then it too will usually respond. There may be an associated iron deficiency which will require the use of iron. There has been some difference in the findings of British and American workers in regard to the anæmia of sprue and its response to folic acid. Davidson, Girdwood and Innes[11] found that folic acid did not completely relieve the macrocytic anæmia in the sprue syndrome; some of their patients showed a subsequent response to proteolysed liver. They concluded that proteolysed liver contained an additional hæmatinic principle not so far identified. Wilkinson[12] had satisfactory results in the treatment of three patients with folic acid; one patient, however, subsequently relapsed and failed to respond to a second course of treatment. Wilkinson concluded that the results obtained by Spies[13][14] and others were due to the presence in their patients of severe nutritional deficiencies as well, a complication not usually seen in Britain. Prolonged use of folic acid in sprue has not been followed by neurological complications. The anæmia and diarrhœa of cœliac disease are not usually relieved by the use of folic acid.

Refractory Megaloblastic Anæmia.

Davidson[15][16] and his colleagues have studied macrocytic anæmias associated with megaloblastic bone marrow, which had proved refractory to a potent refined liver extract. Excluding patients with anæmia associated with pregnancy or the sprue syndrome and also those whose anæmia was suspected of being due to direct dietary deficiency, to malabsorption from the gastro-intestinal tract or to hepatic disease, they found many patients whom they classified as suffering from idiopathic refractory megaloblastic anæmia. They consider that some of these patients may suffer from the sprue syndrome without diarrhœa, or from some other form of alimentary dysfunction. It was in these cases that they used proteolysed liver with good results, and subsequently folic acid with

equal success. As points of differentiation clinically from pernicious anæmia, they noted the absence of acute glossitis and objective signs of involvement of the central nervous system and an absence of enlargement of liver and spleen. The failure to respond to potent purified liver extract in adequate dosage was the only differentiating point from true pernicious anæmia in those cases in which histamine-fast achlorhydria was present. Many patients had free hydrochloric acid in the gastric juice and their condition conformed to the diagnosis of acrestic anæmia (Israels and Wilkinson[17]). As proteolysed liver contains only 0·8 milligramme of folic acid per ounce, Davidson and his co-workers feel that it contains some other hæmatinic substance as yet unidentified. At present they treat all patients suffering from megaloblastic anæmia at first with parenteral injections of liver extracts; if this treatment is unsatisfactory they use folic acid; if this fails they give one ounce of proteolysed liver daily.

Aplastic and Hypoplastic Anæmias.

When aplastic and hypoplastic anæmias have failed to respond to the usual substances used intensively, they require treatment by repeated blood transfusion; transfusions may need to be repeated over a long time in the hope that bone-marrow recovery will ensue; especial care must be given to cross-matching with donor blood. After prolonged therapy without improvement, splenectomy may be considered. Most investigators have found no benefit from the use of folic acid. However, Gendel[18] treated three patients with good results, using large doses (200 to 300 milligrammes daily). In all such cases a careful investigation for the ingestion or action of toxic substances should be made.

Splenic Anæmia or the Banti Syndrome.

It is now widely appreciated that splenic anæmia is usually associated with obstruction to the portal venous flow; this obstruction may be intrahepatic or extrahepatic. An intrahepatic cause is most frequent from cirrhosis of the liver and sometimes from schistosomiasis; the anæmia is partly due to the hypersplenic effect of the enlarged spleen, which may cause leucopenia and thrombocytopenia as well. Removal of the spleen has been disappointing in the past, because the portal venous pressure may again build up, with recurrence of hæmatemesis. A notable advance in treatment has been the porta-caval anastomotic operation of Blakemore.[19]

Other Advances.

Interesting recent advances, although not directly related to the discussion, are the use of aminopterin, a folic acid antagonist, in the treatment of acute leuchæmia;[20] *ex sanguino* transfusion for acute leuchæmia;[21] and urethane in chronic leuchæmia.[22]

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SOME PROBLEMS IN THE SURGERY OF THE GALL-BLADDER.[1]

By VICTOR HURLEY,
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THERE are many debatable problems in the investigation, diagnosis and treatment of gall-bladder disease which will repay discussion. Reference should also be made to some of the recent biochemical work in this field—particularly in regard to liver function, and the disorders of the normal physiological processes which may be associated with gall-bladder diseases and their sequelæ. In general, so long as the disease—usually an infection—is confined to the gall-bladder, it does not gravely endanger life. The situation becomes more serious when the trouble extends beyond the gall-bladder to the biliary passages, liver or pancreas. Sometimes, however, the patient's safety may also be threatened by local extension of infection from the gall-bladder so as to involve the peritoneum and viscera in its neighbourhood.

ANATOMY.

It is not proposed to discuss the anatomy in detail, but it should be emphasized that a considerable number of variations in the normal arrangement of ducts and vessels may occur, and these should be constantly borne in mind at operation if serious difficulties or disasters are to be avoided.

PHYSIOLOGY.

One or two points only in the physiology will be mentioned. The function of the gall-bladder in absorbing water from the bile and adding mucus, thus concentrating its contents, is well known. The outflow of the bile from the gall-bladder is controlled by a regulating mechanism at the lower end of the common bile duct, and this is not accomplished by movements of its wall alone. Although bile flows into the duodenum in the fasting state, the amount is greatly increased by the taking of food (for example, the

[1] President's address, delivered before the Section of Surgery, Australasian Medical Congress (British Medical Association), Sixth Session, Perth, August, 1948.

fatty meal in cholecystography). There are also muscle fibres in the common bile duct which have been shown to contract.

Pathological Considerations.

At the time when patients present themselves, infection of the gall-bladder and gall-stones are frequently found in association. Usually, however, infection precedes the formation of gall-stones, and it is now generally accepted that this infection is usually blood-borne and intramural to begin with. The infecting organisms are most often streptococci, *Bacterium coli* or *Bacillus welchii*. The early attacks of infection are mild and usually subside. However, they tend to recur, and as time goes on with increasing frequency and severity, and are generally followed by the formation of gall-stones.

When these have formed, not only are further attacks of infection more likely, but the stones may obstruct the cystic duct, set up biliary colic or pass into the common bile duct. If the cystic duct remains obstructed in the presence of acute cholecystitis, an empyema of the gall-bladder often results, and the passage of stones or the spread of infection from the gall-bladder to the common bile duct opens the way to ascending cholangitis with involvement of the liver and its important functions. In addition, pancreatitis of varying degrees of severity may occur and gravely complicate the position.

On the other hand, certain types of gall-stones may form as a result of disorded metabolism and independently of infection. These stones are well tolerated by the gall-bladder, and may give little or no indication of their presence unless they produce obstruction of the cystic duct. This is also sometimes true of stones resulting from infections which have been so mild that the patient has not sought medical advice. These so-called "silent" stones may be found at operation for other unrelated conditions in the abdomen or on X-ray examination or *post mortem*.

Diagnosis.

The diagnosis of pathological conditions of the gall-bladder has been rendered much more reliable since the introduction of cholecystography. By this means, together with the history and clinical examination, the diagnosis of a diseased gall-bladder can usually be made with reasonable certainty. Unfortunately we still need reliable methods for estimating accurately the function and efficiency of the liver, which are often of vital importance in determining the outcome of treatment.

Tests of Liver Function.

Accurate methods for estimating liver function would also be of the utmost value in the diagnosis of liver conditions, particularly in the recognition of those cases in which medical treatment is indicated—such as cases of so-called "catarrhal jaundice", now more commonly called infectious or non-suppurative hepatitis.

This condition in the acute form may be associated with rise of temperature and tenderness over the liver, with jaundice, and so may simulate infections of the gall-bladder or biliary tract. Infectious hepatitis is due to a virus infection, and the condition of homologous serum jaundice, which resembles it, is due to a somewhat similar virus. Owing to the long incubation period, the recognition of these cases may be missed; in infectious hepatitis the incubation period is from twenty to forty days, and in homologous serum jaundice from two to three months.

Chronic hepatitis also occurs and may simulate gall-bladder conditions. If removal of the gall-bladder is carried out, the symptoms are not relieved.

Ian Wood and his associates have recorded the results of many of the biochemical tests used to estimate liver function in a recent series of cases. The tests employed were the Van den Bergh test for the bilirubin content of the blood serum, and also estimations of cephalin flocculation, alkaline phosphatase content, total serum protein content, albumin-globulin ratio, hippuric acid excretion and prothrombin time. The tests taken together are of much help in diagnosis, but atypical results are not infrequently encountered. The cephalin flocculation test seems to be the most informative single test in the diagnosis between acute infectious hepatitis and obstructive jaundice from stone or carcinoma. The Van den Bergh test always gives a prompt direct result when there is a sufficiently high concentration of bilirubin in the serum, and even a strongly positive direct reaction does not necessarily indicate obstruction of the bile ducts outside the liver by stone or tumour. The quantitative Van den Bergh test, however, often enables jaundice to be detected before it is manifest on inspection of the patient, and the progress of a jaundiced patient can be followed by serial estimations.

Information about the condition of the liver may be obtained by a liver biopsy, which will be discussed by a later speaker.

Clinical Considerations.

For the purposes of discussion five groups of cases can be recognized; these represent the progressive stages which may develop from the initial pathological condition of the gall-bladder.

Group I.

Group I consists of cases in which the disease is limited to the gall-bladder, with no evidence of its obstruction or of spread of infection beyond it. In the early stages the symptoms are mild and chiefly referable to the stomach, while the local signs referable to the gall-bladder may be slight and difficult of detection. Discomfort after meals of a flatulent type with a feeling of fullness, particularly after the taking of fatty foods and other articles of diet, is the usual story. This is particularly significant in middle-aged, overweight patients of either sex, although the condition is not infrequently met with in young people, and also in those of spare build. The demonstration of local tenderness on deep pressure beneath the right costal margin at the end of full inspiration, together with the history and the results of X-ray examination, will establish the diagnosis in most cases.

In some patients the dyspeptic symptoms take on a certain periodicity not unlike those of duodenal ulcer. Sometimes the two conditions exist together. In a doubtful case, if the results of cholecystography are inconclusive, an opaque meal examination is advisable, particular attention being directed towards the possibility of duodenal ulcer. Examination of the stools for occult blood is also advisable.

In dealing with this first group the question of operative interference should be considered, particularly when regulation of diet and medical treatment have failed to give relief. However, it not infrequently happens that when the gall-bladder is exposed at operation it does not present definite evidence of infection, and stones cannot be felt within it.

It has to be remembered that small, soft stones or biliary mud and grit may escape detection, and also that a "strawberry" gall-bladder, the result of cholesterosis, may also be missed. In such cases the gall-bladder is abnormal and probably responsible for the patient's symptoms, and if left, may require removal later because of persistence of the symptoms. If, therefore, the clinical history and X-ray findings have indicated the gall-bladder as the site of the symptoms, it is better to remove it. However, it has to be admitted that in all these doubtful cases the condition is not completely relieved by the removal of the gall-bladder, the symptoms being not uncommonly due to chronic hepatitis or cirrhosis of the liver of various types.

It has also to be borne in mind, as Moynihan first emphasized, that there is a relationship between what he called the abdominal triad—diseased gall-bladder, peptic ulcer and disease of the appendix.

In these doubtful cases it is therefore advisable that the stomach, duodenum and appendix should be carefully inspected.

The early attacks in the cases in this group do not produce the picture of an acute emergency, so that the question of urgent operation does not arise.

Group II.

Group II consists of cases in which the cystic duct or neck of the gall-bladder becomes obstructed, usually by stone. In this group there is usually a history, as in Group I, of an antecedent dyspepsia of gall-bladder type; but the attack for which the patient presents for treatment is acute in onset. The distended gall-bladder may soon be felt as a smooth, tense, tender swelling below the liver; but it may be difficult to detect because of rigidity of the overlying abdominal muscles, especially if the patient is stout. Shivery feelings with some rise of temperature may be present soon after the onset, and mild jaundice may be noted by the third or fourth day from associated cholangitis or from the pressure on the common bile duct of a large stone in the cystic duct. Necrosis of the wall of the gall-bladder may occur and may extend through it, or actual perforation may follow. The adjacent viscera and omentum may become firmly adherent to the gall-bladder with or without abscess formation, or in the more fulminating cases spreading peritoneal infection may result.

More often, however, the obstruction is partly relieved by the second or third day, either by movement of the stone or by lessening of the swelling of the mucous membrane, and the infection begins to subside.

The management of patients with obstruction of the gall-bladder is open to some difference of opinion. Some regard acute obstructive cholecystitis as a surgical emergency, while others defer operation until the acuteness of the infection and the obstruction have subsided, as they will in most cases.

The technical difficulties and dangers of cholecystectomy are greater when the gall-bladder is acutely inflamed and are due to the increased vascularity and friability of the gall-bladder as well as of the liver tissue with which it is in contact. In addition, the liver function may be temporarily depressed as a result of the infection. From the second or third day onwards these difficulties increase, and generally it is the practice in most hospitals to admit patients with acute cholecystitis to the medical wards, where they are treated until the infection subsides. This policy would appear to be justified by results.

There should not be a hard and fast rule in these cases, and it would seem best not to defer operation any longer if the symptoms and signs continue unabated or are more severe by the third day.

For elderly patients and for "poor risks" cholecystostomy may be the operation of choice with a minimum of anæsthesia or possibly with local anæsthesia, nothing more being done than to open the gall-bladder and drain it after removal of the obstructing stone or stones.

When operation is deferred until the infection has subsided, some consideration should be given to the length of time which should elapse. Varying periods from ten days up to three months or longer have been advised. Most surgeons operate about two or three weeks after the attack has subsided, but the evidence of subsidence may be very deceptive.

It also not infrequently happens that as the condition appears to be subsiding a further acute attack may occur.

Group III.

Group III consists of cases in which attacks of biliary colic recur. In these the diagnosis presents little difficulty. The situation of the pain in the upper right quadrant of the abdomen radiating through to the right scapular region is usually recognized as showing it to be of gall-bladder origin. The attacks may occur at varying intervals, sometimes every few days, while weeks, months or even years may intervene between attacks. They usually increase in frequency and severity as time goes on, and between attacks flatulent dyspepsia is usually present.

Cholecystitis is usually associated with the attacks and readily extends beyond the gall-bladder to the biliary tract with resulting cholangitis. As the gall-bladder is not completely obstructed, it does not become distended and palpable, but tenderness and rigidity over the gall-bladder are demonstrable in most cases. Jaundice, usually not of severe degree, may be present in a fairly large percentage of cases, and in this regard it should be remembered that some 25% to 30% of patients with gall-bladder disease who have been jaundiced are found at operation to have gall-stones confined to the gall-bladder and none in the common bile duct. On the other hand, 20% to 25% of patients with stones in the common bile duct, as verified at operation, have not had jaundice at any stage in their history.

Recurring biliary colic is perhaps the most frequent reason for which patients seek medical aid, and operation offers the only relief. The diagnosis, which is usually evident on clinical grounds, may be confirmed by cholecystography.

In the types so far considered reference has been made only to the direct local manifestations and the results of acute infections of the gall-bladder. There are certain other related conditions which should be mentioned.

Carcinoma of the Gall-Bladder.

Carcinoma of the gall-bladder is almost always associated with gall-stones, and there is usually also a history of gall-stone attacks preceding the carcinoma. Graham has stressed the frequency of this association between gall-stones and subsequent carcinoma, stating that it occurs in 9% of cases. It would seem that there is a definite causal relationship between the two conditions. It is rarely possible to remove a carcinomatous gall-bladder satisfactorily, because at the time of operation infiltration has usually occurred into the liver tissue. This is therefore an important reason why a diseased gall-bladder should be removed, particularly if subject to recurrent attacks of infection.

Diagnosis from Acute Cardiac Conditions and the Association of Cardiac Symptoms.

It is sometimes difficult to diagnose acute cholecystitis or a severe attack of biliary colic from a coronary occlusion. The infrasternal or retrosternal pain of sudden onset—agonizing in character, with evidence of shock—may be very similar, making it difficult to determine whether the seat of the trouble is above or below the diaphragm. The history may help in the diagnosis and an electrocardiogram may show evidence that the myocardium has been involved. After the attack has subsided cholecystography may assist in the diagnosis.

In another different type of case, in which a diseased gall-bladder is present, the myocardial involvement is chronic and the patient complains of palpitation, irregular heart action, breathlessness or angina-like pain on exertion. In some cases these symptoms seem to be reflex in origin, while in others they appear to be due to a toxic action on the myocardium associated with the infected gall-bladder. Close inquiry into the history followed by cholecystography may arouse suspicion that the gall-bladder may be responsible for the cardiac symptoms. Removal of the infected gall-bladder in such cases is often followed by relief.

Group IV.

Group IV consists of cases of stone in the common bile duct. The clinical picture in typical cases is readily recognized, but many atypical cases occur. In typical cases the features are recurring colic, rise of temperature (remittent in type and often associated with shivering and sweating), and jaundice, which, while being pronounced, is not usually extreme. The jaundice may show variations in degree, an increase in the jaundice being especially likely after an attack of colic. Involvement of the liver with cholangitis is evidenced by this clinical picture, and as times goes on the patient looks ill, with loss of weight and strength. An antecedent history of gall-bladder infection or stones is usually obtained.

In other cases no such preceding history of gall-stone attacks or colic is available; the pain may be mild and followed by jaundice, which is progressive, and so presents a clinical picture hardly to be distinguished from obstructive jaundice due to malignant disease of the pancreas

or biliary ducts. However, jaundice may be entirely absent throughout the progress of the case, and the possibility of stone in the common bile duct may not be suspected. Even when it is specially sought, such a stone may still be missed at operation, especially if it is located at the lower end of the duct, and this can occur even after the duct has been opened and probes and sounds have been passed.

The continued presence of stones in the common bile duct with recurring attacks of cholangitis causes serious damage to the liver, and operation for their removal should not be unduly delayed. It is better if operation can be performed in an interval between attacks, when jaundice and evidence of infection are lessened or in abeyance. However, often no such interval may occur and the symptoms may continue, while in other cases attacks follow one another at short intervals, so that operation may have to be undertaken after a period of waiting, during which the patient's condition has still further deteriorated. Accurate prediction of the course any particular case will follow is impossible, and the policy of delay often causes more risk to the patient than early operation in the presence of jaundice and infection. With adequate pre-operative treatment operation can be carried out at an earlier stage than was previously the practice, and with reasonable confidence.

In all operations for gall-stones, with the possible exception of those for acute obstructive cholecystitis, the common bile duct should be inspected and also palpated.

Stones in the supraduodenal part of the duct are readily felt, but lower down, where the duct traverses the head of the pancreas, it is more difficult to detect them or to distinguish them from the hard or nodular feel of carcinoma or chronic pancreatitis. Before opening the duct it is advisable to verify that it is actually the duct by aspirating it with a fine needle and syringe. In addition, further confirmation of the presence of contained stones is obtained if the bile is turbid or of pale colour, or if it contains small pieces of grit or biliary sediment. In advanced cases of obstruction of the common bile duct, usually due to carcinoma, the bile in it may be colourless; this so-called white bile is of grave significance as indicating an extreme degree of damage to liver function.

If it is decided to open the duct, this is done after due provision against escape of its contents by the use of packs and a sucker. It is cleared of contained stones with forceps and scoops, and sounds are passed to establish that its lumen has in fact been cleared. It is essential that the lowermost stone be located and removed. Most surgeons drain the duct with a small tube or rubber catheter, but in MacCormick's operation, after sounds have been passed into the duodenum, the incision in the duct is sutured and reliance is placed on internal drainage of the bile by way of the normal route.

Some surgeons advocate the routine opening of the duct in all cases of gall-stones, but this adds to the hazards of operation in bad "risks", and for stout patients and others in whom the technical difficulties may be great. Thus while it is admitted that an occasional stone in the duct may be missed by failure to open it, it would seem preferable to open it only if there is some definite evidence of the probable presence of contained stone.

Sometimes if it has been decided to explore the duct this may be done with advantage by opening the cystic duct and prolonging this incision into the common bile duct.

Finally, it is advisable in any case of obstructive jaundice, if the least doubt exists as to the cause of the obstruction, that the patient should be given the chance of an exploratory operation. The silent stone can be extremely silent, and the end result of a carcinoma of the pancreas is inevitable.

Group V.

Group V consists of cases associated with pancreatitis. While acute pancreatitis occurs independently of acute cholecystitis, it sometimes results from it or develops concurrently with an infection commencing in the gall-bladder. The association of acute pancreatitis with a stone at the ampulla of Vater is a rare occurrence.

The association of pancreatitis with a gall-bladder infection may be suspected from the site and intensity of the pain, which, having commenced in the mid-line, extends to the left below the costal margin towards the left flank. Tenderness and muscular rigidity are present in the same distribution, and tenderness on pressure beneath the tenth left rib posteriorly is especially significant. The pain is more continuous and severe than in cholecystitis, the patient is more shocked, and sedatives in large doses may fail to relieve the pain. Estimations of the urinary diastase output in the first three or four days may help to confirm the diagnosis of pancreatitis.

If the clinical evidence indicates that the main infection is in the pancreas, operation should be withheld. It is doubtful whether surgical treatment directed to the pancreas with the object of providing drainage achieves any real good. If operation has been undertaken and associated cholecystitis or stone in the gall-bladder has been found, cholecystostomy after removal of the stones is advisable, but its influence on the pancreatitis is rather problematical. Chemotherapy, particularly with adequate and full doses of penicillin—especially during the first few critical days—seems to influence the course of the pancreatitis favourably.

If the pancreatitis has been severe and the patient recovers, some necrosis or sloughing of the pancreatic tissue may occur and be manifested later by a swelling in the upper part of the abdomen with the characters of an abscess or cyst of the pancreas which requires surgical treatment.

In those cases of pancreatitis which have subsided and in which there is reason to suspect that the gall-bladder was also involved, the latter should be investigated later and cholecystography carried out. If confirmation is thus forthcoming that the gall-bladder is diseased, it should be removed.

PRE-OPERATIVE TREATMENT.

The pre-operative treatment of patients with no evidence of either obstruction or infection of the biliary tract does not differ from that of other patients about to undergo other abdominal operations. Overweight and flabby patients, whose condition is not urgent, can be rendered more fit by dieting and a programme of exercise and training during the period of waiting for admission to hospital.

In jaundiced patients some degree of infection of the liver as well as of biliary obstruction is usually present and the function of the liver is affected. Careful pre-operative treatment is necessary to make operation safer for these patients.

Carbohydrate metabolism is interfered with, fat metabolism is impaired, and there is also deficient prothrombin formation, with hypoprothrombinæmia and increased tendency to hæmorrhage. The interference with carbohydrate and fat metabolism may give rise to a condition of acidosis. Dehydration of the tissues may also be a factor. The free administration of fluids and readily assimilable carbohydrates, particularly glucose, is required, and it is preferable to give these whenever possible by the natural routes. In urgent cases or in those in which the necessary amounts cannot thus be assimilated, treatment will require that fluids be given intravenously, usually as dextrose-saline or saline solution. A daily chart showing fluid intake and output should be kept. Care should be taken not to overdo the intravenous fluid administration and so cause waterlogging of the tissues, particularly of the bases of the lungs in elderly patients and in "poor risk" patients. Regular examination of the urine will determine the position regarding acidosis, and insulin may need to be given as well as glucose to combat this.

Vitamin *K* is also concerned with prothrombin in the process of the arrest of hæmorrhage. If bile fails to reach the intestine, as in cases of obstructive jaundice, there is deficient action of prothrombin and vitamin *K*, because bile is necessary for the absorption of the vitamin *K* from the intestine, which, when naturally occurring, is fat-soluble.

Water-soluble preparations of vitamin *K*, such as "Synkamine" and others, are effective when given by the

mouth or by injection even in the absence of bile salts. Vitamin *K* is given for one or two days before operation and for four or five days post-operatively. Bile salts, usually in capsules, may also be given by the mouth.

The blood group of these jaundiced patients should also be determined before operation, so that no time need be lost in seeking a suitable blood donor if a transfusion is required.

ANÆSTHESIA.

A well-given light ether anæsthetic is very satisfactory in most cases. Sick, "poor risk" patients will not tolerate well a prolonged operation with a poorly given anæsthetic. Adequate relaxation is necessary at two stages of the operation—during the exposure of the common bile duct and the structures in its vicinity, and also during closure of the abdomen. The use of the Oxford vaporizer is a satisfactory method, being economical in the amount of ether used and permitting an even anæsthesia.

OPERATION.

Of the many incisions which have been suggested, two are chiefly employed: a subcostal incision, such as Kocher's, and a right paramedian incision. In recent years Kocher's incision has come increasingly into favour. It is satisfactory in most cases, particularly in operations on stout patients, on those with a wide costal arch, and on those in whom the gall-bladder is well out towards the flank. It was at one time thought that it left a weaker scar with a higher incidence of incisional hernia than the paramedian incision, because muscle fibres and usually one at least of the intercostal nerves were divided. In actual practice this is not found to be so. The incision is also easy to close, and as it interferes less with the movement of the abdominal muscles post-operative chest complications are less likely.

In the operation of cholecystectomy, as usually carried out and taught, the cystic duct and vessels are secured as a first step. It is essential in doing this that everything be clearly seen and identified before any structure is tied or cut. The results of damage to the common bile duct, the common hepatic duct or the right branch of the hepatic artery are so serious that the utmost care should be taken at every step to ensure their safety. It has to be borne in mind that, not infrequently, there is some departure from the usual anatomical arrangements.

One must be prepared occasionally, if the approach via Hartmann's pouch proves difficult, to proceed with the removal of the gall-bladder from the fundus or to look at the situation from the upper and medial aspect of the neck of the gall-bladder, as the removal may be easier and safer from above than from below.

I have found the use of a series of polished metal retractors of varying length and width most useful. The light from the overhead operating light can thus be directed accurately to show clearly the structures in the depth of the wound and to keep them in view throughout.

POST-OPERATIVE COMPLICATIONS.

Post-operative complications will be only briefly touched on. Vomiting and post-operative distension with gas pains are rather more common than after most other abdominal operations. In ordinary cases, the administration of fluid by the rectum for the first day or two usually meets the patient's need for fluids until sufficient can be given by the mouth. Post-operative intravenous therapy may be required in special cases and has been discussed under pre-operative treatment.

Deep breathing, early movement and exercises are instituted as soon as possible after operation, in order to minimize the risks of post-operative chest infection and thromboses.

A watchful eye should be maintained for the earliest evidence of thrombosis, particularly in the calves of the legs. If this is suspected, dicoumarol may be used, the dosage being determined by regular estimations of the prothrombin content of the blood. Heparin may also be employed. It is not yet possible to state definitely the result of treatment, but so far as present experience goes it is difficult to correlate the daily prothrombin findings with the clinical progress—wide and unpredictable variations seem to occur.

END RESULTS.

The results after operation are good in the great majority of cases. The most striking improvement occurs after operation in cases of obstructive cholecystitis and after removal of stones from the common bile duct. In those cases in which the abnormal condition of the removed gall-bladder has been doubtful or indefinite, there may be persistence of some of the symptoms of dyspepsia, flatulence and pain about the liver. These symptoms most often arise from cirrhosis of the liver or chronic hepatitis of various kinds.

Stones sometimes recur in the stump of a cystic duct or in the common bile duct. In regard to the latter, it seems established that stones can form occasionally in the biliary passages within the liver and that their presence is not always due to overlooked stones at an earlier operation on the duct.

A disconcerting happening is the occasional early recurrence of an attack of pain soon after an apparently successful cholecystectomy with a normal post-operative course. It may, of course, be due to an overlooked stone, but it sometimes seems to be due to the passage of some biliary mud, debris or other foreign material passing down the ducts, as the attack may quickly clear up and not be repeated. It is rather doubtful whether the condition of so-called biliary dyskinesia can be regarded as an adequate explanation of such cases.

A SUBSTITUTE FOR BUTTERMILK AND ITS USE IN INFANT FEEDING.[1]

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BUTTERMILK has been used for a very long time on the Continent of Europe, where it has an established reputation in the treatment of infants with nutritional disorders. It has never been popular in the United Kingdom or in Australia. Perhaps if its advantages were better known, it might be more widely used in this country.

The first paper on this subject was published in Holland in 1865 by Ballot.

Originally "natural" buttermilk, a by-product of the dairy, was used, but this was crude and unreliable. "Prepared" buttermilk was a technical advance, the separated milk being first heated to destroy pathogens and organisms of the fæcal type, after which it was soured by a "starter"—usually an inoculation of a culture of *Streptococcus lacticus*.

The use of buttermilk was empirical. Satisfactory theoretical reasons for its success in practice were lacking, but there was general agreement that it was well tolerated and that its use resulted in a beneficial clinical effect on infants with bowel disorders. Its disadvantages, however, were considerable. They were as follows.

1. The composition and acidity were variable and the taste was unattractive, owing to the varying quality and strength of the "starters" used.

2. The fat content was too low and variable—too low for prolonged use, and varying from 1% or 2%, when a hand churn was used for separating, to an almost fat-free product if a centrifuge was used.

3. The food was easily contaminated, though this could be corrected by boiling after the addition of 1·5% of cereal, the added cereal preventing the coagulation which normally follows boiling without this addition. This boiling destroys the lactic acid bacilli without in any way affecting the value of the food, which suggests that its clinical success is not due to the organisms themselves. Lactic acid bacilli, in any case, cannot be recovered in

[1] Read at a meeting of the Section of Pædiatrics, Australasian Medical Congress (British Medical Association), Sixth Session, Perth, August, 1948.

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the stools, and probably do not long survive in the alkaline medium which they encounter after leaving the stomach.

4. The most serious disadvantage, preventing its wide adoption, was the fact that its preparation in the home was difficult and troublesome.

With the introduction by Marriott of lactic acid milk, a possible alternative to buttermilk seemed to be available, namely, skimmed lactic acid milk. There remained, however, the difficulty of regulating the fat content, accurate skimming of milk being very difficult, especially in the average home. Most of the devotees of the older preparation held that skimmed acid milk, even if accurately separated, did not give comparable results.

The manufacture and marketing in Europe of tinned dried buttermilk seemed to abolish most of the difficulties previously encountered, and made the use of ordinary buttermilk obsolete wherever the tinned product could be obtained. Although there were other brands available, the Swiss preparation, "Eledon", which was widely used in Europe, was the one selected for import into Australia. Its composition, after reconstruction, was as follows: protein 3%, fat 1·4%, carbohydrate 4%, mineral 0·7%, acidity pH 6. It had a caloric value of twelve Calories per ounce. Its fat content was satisfactory and constant, but there was a tendency for the acidity of the food to increase with keeping. This happened even in Europe with a moderately fresh package, and led to the practice, in some clinics, of daily titration of a sample and correction of the acidity. Although its flavour does not appeal to the sophisticated adult palate, "Eledon" is well taken by young infants, even when unsweetened. Older babies prefer a sweet milk to any acid formula.

The onset of World War II, and the consequent limitation of imports, brought to an end some years of extensive experience with "Eledon".

The principal objective of this paper is to report the result of efforts to evolve an efficient substitute, and to discuss the formula of what shall be called "B.M.S." (buttermilk substitute), with the indications for its use in view of experience with it in the case of many hundreds of infants over the last few years.

The ingredients for its preparation are as follows: evaporated milk ("Ideal") six ounces, water 24 ounces, milk protein powder ("Protosol")[1] half an ounce (two tablespoons), lactone syrup three-quarters of an ounce. To prepare the food the "Protosol" is dissolved in hot boiled water at night, and is then covered and allowed to cool till the morning when the cold "Ideal" milk is added. The lactone syrup is then slowly stirred in in the usual way. This makes thirty ounces of the food which has the following formula: protein 3·2%, fat 1·6%, carbohydrate 4·5%, mineral 0·47%, acidity pH 4·88. It has a caloric value of 14 Calories per ounce.

Extra carbohydrates, such as lactose, cane sugar, "Dextri-Maltose" (or "Maltogen") or cereals, can be added to this food in any desired proportion, just as was the custom with dried buttermilk. If there has been an acute upset it may be advisable to avoid lactose supplement and preferable to use a less fermentable sugar, such as cane sugar or "Dextri-Maltose". The addition of carbohydrates is made gradually, when the acute phase of the upset is passing, in order to add to the food value. A 5% carbohydrate addition raises the caloric value to 20 Calories per ounce.

Extra vitamins are added as a routine, from the start, at all ages, for example, "Pentavite" (fifteen drops) and fruit juice (one to two ounces of orange juice).

This formula was arrived at after a good deal of experiment. The variable composition and quality of cow's milk seemed to make it unsuitable. Dried milk was rejected because of the difficulty of accurate measurement. Evaporated milk was preferred; its use resulted in a more consistently reliable, elegant and tasty preparation and gave better results. Dried skim milk powder ("Capstan" brand) was tried for raising the protein content, but was abandoned because its use led also to raised lactose and mineral percentages and, perhaps because of this, tended to produce loose stools. "Protosol" is now temporarily unobtainable so it has again been necessary to improvise with other proteins. Commercial casein, as used by Dr. F. W. Clements in Canberra, makes a fairly satisfactory protein, but is an unrefined, non-sterile product, which should be boiled when dissolved in the water. Casein hydrolysates ("Casydrol" and "Pronutrin") have also been used. They contain 50% of lactose and are expensive.

"B.M.S." then is a sterile food of better flavour and more constant acidity than buttermilk or "Eledon". It is easy to make in the average home. It is readily taken, easily digested and well tolerated by infants. Its high protein content is well modified, being "denatured" by processing, drying and acidification. The acid medium is unfavourable to the growth of pathogens and is thought to stimulate gastric secretions and assist protein splitting. The fat content is constant and moderately low, but not so low that the food cannot be given for fairly long periods without the addition of more fat. When it is desired to raise the fat in the diet I prefer to do this by changing over, one feed at a time, to a richer food. Butter-flour preparations can be added, but care must be taken that the patient is free from diarrhœa. In the presence of nutritional upset the dietary fat is probably least well borne of the food elements, and so it is well to be conservative in making the fat additions. Especially is this so in a hot climate. The carbohydrate percentage, too, is moderately low and this fact, combined with the acid medium and the high protein content, minimizes fermentative processes.

The mineral content is moderate, being midway between 0·2%, the figure for breast milk, and 0·7%, the figure for both cow's milk and buttermilk. Finkelstein's protein milk was based on the alleged damage done by the whey salts. His formula halved the fat, carbohydrate and mineral content of buttermilk and kept the protein content high by the redissolving of more protein.

"B.M.S." can be regarded as a temporary medicinal food, but, if its limitations are kept in mind, it can be used as the basis of the feeding for long periods. The formula meets most of the feeding indications which are generally accepted for nutritional upsets and infections. It has been used extensively in the following types of case.

1. In the treatment of newborn and premature children and weaklings. In these cases it can be given either as a supplement to, or as a temporary substitute for, breast milk, or as a transition food preliminary to artificial feeding. Lactose is commonly used for carbohydrate addition at this age period.

2. In cases of acute dyspepsia, with or without infection. In such cases, after the usual preliminary starvation, it is given in increasing quantities. Carbohydrates are added when the acute phase of the upset is passed, and later the permanent food is substituted step by step.

3. In cases of diarrhœa, acute or chronic, with enteral or parenteral infection. After successful treatment of the initial acute phase, and when it is desired to resume feeding with some form of milk, unsweetened "B.M.S." can be started in gradually increasing quantities. It can be given in conjunction with an apple diet. Foods other than milk are given if the infant is old enough, namely, cereals, broth *et cetera*. Carbohydrates other than lactose are added to the "B.M.S." and the transition to the permanent milk food is made later as the condition progresses. The logical sequence is to a skimmed lactic acid milk formula. Buttermilk or "B.M.S." is especially to be recommended as a transitional food in all forms of "gastro-enteritis". The pathogens of infectious diarrhœa mostly require an alkaline medium and tend to die out in an acid medium. The prolonged feeding of subjects of enteritis with diets having a low protein content and rich in carbohydrates and starches gives poor results, diarrhœa being likely to persist, with fermentation, the result of sugar or starch injury. Weight gains are poor and convalescence is

[1] Since this paper was prepared an imported brand of "Protosol" (soluble milk protein) has been marketed in Australia by Glaxo Laboratories, Limited. This is a much lighter and more flocculent preparation and requires eight packed medicinal tablespoon measures to make the half-ounce by weight—just four times as much by volume as of the older preparation.

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prolonged in the presence of protein starvation, the infant tending to drift into a dystrophic state. Under this type of feeding also, lowered resistance of the infant results frequently in secondary complications, such as delayed healing of an ulcerated colon and secondary infections of the skin, ears and respiratory or urinary tract. Dysentery is to some extent a self-limited disease, and, as one of the objectives of treatment is to maintain, as far as possible, the state of nutrition of the victim, adequate Calories must be given. "B.M.S." admirably fulfils the dietetic indications in these cases.

4. In cases of malnutrition or dystrophy and of chronic fat dyspepsia. "B.M.S." is a satisfactory food to use for fairly long periods in these cases. I have found it, perhaps, the food of choice to start with, being of low fat and carbohydrate content and unlikely to give rise to fermentative troubles. Its high protein content is most easily digested and tolerated. The food value can be advanced by the steady addition of mixed sugars and cereals, and extra foods other than milk are added to the diet at the earliest possible time compatible with the child's age.

5. In cases of milk allergy. The food can be given for long periods to young infants with milk intolerance or dermatitis. In these cases, too, foods other than milk are added as early as possible, in order to limit the milk intake.

6. In cases of certain other diseases, in which a food of high protein and low fat content is desirable, such as congenital steatorrhœa with pancreatic defect, cœliac disease, liver disorders and nephrosis.

Acknowledgements.

In conclusion, I wish to acknowledge the willing and valuable cooperation of the directors of Nestlé's Food Specialties (Australia), Limited, for importing "Eledon" for prolonged trial, and for continuing to supply "Ideal" milk, on prescription, for special infants during the war period, when it was not available generally; also the directors of Glaxo Laboratories (Australia), Proprietary, Limited, for continuing to supply "Protosol" for this work for a considerable time after its manufacture and sale to the general public were discontinued.

Reviews.

PHYSIOLOGY OF THE EYE.

WITH research into the physiology of the eye making such rapid strides, the student of ophthalmology has little prospect of keeping in touch with modern thought unless he keeps a careful eye on many different technical journals. "Physiology of the Eye" has been designed by Hugh Davsen, D.Sc., to meet this special need.[1] As a teacher and research worker with Duke-Elder at the newly founded Ophthalmic Institute in London, he needs no introduction.

After a brief introduction he plunges into the difficult subject of intraocular dynamics. This is his own field, and his exposition creates a favourable impression, enhanced by the remainder of the book. At times the uncritical attitude of the author makes the reader uneasy. He accepts too readily Ascher's views on the aqueous veins, and Troncosco's work on the comparative anatomy of the filtration angle work based on the study of a mere handful of vertebrate eyes. His acquiescence in Detwiler's assertion that Kolmer's droplets in the frog retina are actually retinene is rather surprising. Walls, a very careful retinal histologist, regards them as artefacts. It is a serious criticism in a text-book that the doubtful authenticity of such statements is not stresed, and that they may be too readily accepted by the student.

There is evidence of lack of care in the choice of illustrations. Polyak's modern "General Scheme of the Primate Retina" is found on the opposite page to Duke-Elder's antiquated drawing of the rods and cones. The finer points of histology are easily overlooked by the research worker in physiology, and Davsen is unaware of the carelessness of Granit in his choice of material. The latter's choice of the retina of the turtle as pure cone and of the guinea-pig as pure rod must cast some doubt on the interpretation of his retinograms. Similar criticism applies to the whole field of experimental physiology of vision. Animal eyes are not human eyes, and unless the research worker appreciates the differences in ocular structure in the various species of vertebrates, his experiments are apt to be meaningless.

Whilst the book may not always satisfy the contentious critic, it covers the field of ocular physiology in a manner convenient to the student, and provides a summary of the present healthy activity amongst research workers on the function of the eye.

[1] "The Physiology of the Eye", by Hugh Davsen, D.Sc. (London), with a foreword by Sir Stewart Duke-Elder, K.C.V.O., M.A., D.Sc., Ph.D., M.D., F.R.C.S.; 1949. London: J. and A. Churchill, Limited. 8½" × 5½", pp. 468, with 301 illustrations. Price: 32s.

ALLERGY.

DR. W. T. VAUGHAN died before he had completed the revision of his text-book on allergy, and the second edition revised by Dr. J. H. Black has now been published.[1] Dr. Black has aimed at retaining the characteristics of the original text-book, but has brought many chapters up to date and has coopted specialists to write on such subjects as pollen surveys, fungous infection and measurement of vital capacity. Of especial interest is the historical chapter with portraits of several of the pioneers.

This book is formidable in size and the bibliography is very extensive, so that the index contains thirty-six pages of closely printed references to the literature. The accumulation of these references must have entailed much work, but a great deal of the information is so poorly digested that it would be of little use to the uninitiated reader. One would expect a book of 1132 pages to be very comprehensive, but, although two pages are devoted to notes on the cultivation of silk, no adequate information is given regarding the very important problem of idiosyncrasy to penicillin. A section on methods of testing with this substance and on interpretation of results would have been most useful.

More than 160 pages are devoted to food allergy and much space is devoted to elimination diets and to special cookery recipes. There is no doubt that food allergy is important and very striking in certain cases, but many authorities now hold the view that in adults it is of minor importance compared to allergy to air-borne allergens. These chapters are too uncritical and the novice may easily be led to waste time in unproductive investigations for many of his patients. The author admits that skin tests for food allergy are unreliable, and it is obvious that stringent and repeated trials of suspected food should be made before a decision is made that the patient is allergic to it.

Effective treatment depends obviously on accurate knowledge of causes, and yet, although there are sections on the history, pathology, symptoms and treatment of asthma, there is no compact section on the causes of asthma. The section on prognosis is hardly adequate and there is no mention of the poor outlook for aspirin-sensitive patients.

Despite these criticisms the book contains many fascinating sections and the reader with leisure will find much of interest. The printing, illustrations and format are excellent.

[1] "Practice of Allergy", by Warren T. Vaughan, M.D., revised by J. Harvey Black, M.D.; Second Edition; 1948. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 10" × 6½", pp. 1156, with illustrations. Price: £5 12s. 6d.

TREATMENT BY DIET.

THE handsome and compendious text-book of "Treatment by Diet" by C. J. Barborka, Assistant Professor of Medicine in the North Western University, was first published in 1934 and now appears in its fifth edition.[2] The work is divided into several parts, dealing with diet in health, the application of diet therapy, diet in disease, routine hospital diets and pre-operative and post-operative dietary management. At the end is an appendix containing tables of the nutritive values of foodstuffs and a large bibliography.

The section on diet in health is concerned largely with an up-to-date account of the vitamins, containing many tables

[2] "Treatment by Diet", by Clifford J. Barborka, B.S., M.S., M.D., D.Sc., F.A.C.P.; Fifth Edition; 1948. Philadelphia, London and Montreal: J. B. Lippincott Company. Sydney: Angus and Robertson, Limited. 10" × 7", pp. 792, with illustrations, some of them coloured. Price: 75s.

which set out lucidly their known functions, the effects of their deficiency, their concentration in common foods and their prophylactic and therapeutic dosages. An interesting feature of this section is a "typical diet" for an average normal adult weighing 150 pounds (70 kilograms). This diet allows each day 70 grammes of protein, 135 grammes of fat and 230 grammes of carbohydrate, the total caloric value being 2415: it includes daily allowances of 60 grammes (2 ounces) of butter, 60 grammes (2 ounces) of reduced cream, a tablespoonful of salad oil, two slices of bacon and two eggs. In this country at present, where local consumption of certain fatty foods is restricted by law in order to make larger quantities available for export to less fortunate lands, such a diet could not be obtained, and we doubt if it could be obtained by the majority of North Americans, though both Australians and North Americans consume on the average more than 2750 Calories a day, and like to eat a good deal more than 70 grammes of protein per day. The quantities of the ingredients of this diet, as with all the others in the book, are set out in household measures as well as by weight, which the practitioner will find very helpful. This section of the book closes with a chapter on the diagnosis of deficiency diseases. The section on the application of diet therapy is illustrated with coloured plates showing equivalent servings of common foodstuffs.

The section on diet in disease is divided into two subsections, one on diseases in which diet is of paramount importance and one on conditions in which diet is of "varying" importance. In some of the chapters dealing with diseases the author devotes a good deal of space to non-dietary measures of treatment, such, for instance, as the use of antacids in peptic ulcer, and to description of characteristic abnormal physical signs, such, for instance, as the position of the hands and feet in tetany: these matters would seem to be outside the scope of a text-book of this kind, though no doubt it is quite justifiable to mention medication to increase or diminish the appetite for food or to improve digestion. Many of the diets contain much more butter, cream and other fatty foods than even invalids are allowed to have, or can obtain, in this country, except perhaps the inmates of some State-controlled hospitals.

This is a most stimulating book and is bound to renew the interest of each reader in the value of dietary measures in all kinds of medical practice. It even makes the practice of dietetics seem simple. However, the author sounds a very necessary warning when he writes that it is not intended that the diets set out should be used as stock or printed lists for particular diseases and applied to all patients with these diseases, irrespective of particular needs. "The greatest fault of dietetics today is the attempt to use a standard list for each disease for all patients."

A TEXT-BOOK OF OBSTETRICS.

THE seventh edition of "The Queen Charlotte's Textbook of Obstetrics" by members of the clinical staff of the hospital has been published.[1] The whole book has been revised to bring the text into line with methods of obstetrics as practised at the hospital today.

A new chapter on fœtal physiology is based on the recent researches of Barcroft, and an excellent chapter is devoted, for the first time, to the Rhesus factor. A simple outline of present knowledge is given without details of the complexities of nomenclature and the discussion on various clinical aspects is very good. Sections concerning the baby have been rewritten. A new table showing the changes in fœtal circulation following pulmonary respiration is produced and the chapter on premature babies has been revised. The use of modern chemotherapy has been shown to be of value in neonatal infections.

It is good to see that decidual endometritis as a cause of abortion has been omitted, as few hold that pregnancy is likely to occur in the presence of endometritis. There are several recent advances in the treatment of the toxæmias of pregnancy which have been omitted, namely, the value of extra amino acids in *hyperemesis gravidarum*, ammonium chloride for œdema, and magnesium sulphate and hypertonic glucose solution in eclampsia.

The valuable American classification of cardiac disease into four groups has been included in the section relating to heart disease associated with pregnancy. Emphasis is placed on the danger of acute specific fevers. An attack of rubella in the early months of pregnancy is said to give approximately 10% chance of causing some form of congenital abnormality in the fœtus.

No mention is made of the tendency to toxæmia in diabetic pregnancies nor of the value of hormone therapy. The Lövset manœuvre of delivering a breech with extended arms is mentioned, but probably today this method should hold pride of place. Emphasis is now placed on the expectant treatment of *placenta prævia* in contrast to active methods discussed in the last edition. Plugging the vagina as a method of treatment is no longer advocated and Browne's classification into four types of *placenta prævia* is quoted.

It is interesting that mismanagement of the third stage of labour is not given as a possible causative factor in inversion of the uterus. There is a very good chapter on pyrexia in the puerperium, including the value of modern chemotherapy. During the first stage of labour "twilight sleep" and barbiturates are reported to be less used, while pethidine has found considerable favour. New sections include the use of local and caudal anæsthesia and mention is made of trilene as an anæsthetic in the second stage of labour.

Figures show the fall in maternal mortality rate and a table of preventible deaths stresses the urgent need for adequate antenatal care.

This is an excellent book which adequately surveys modern obstetrical methods and it can be strongly recommended to both students and practitioners.

[1] "The Queen Charlotte's Textbook of Obstetrics", by G. F. Gibberd, M.B., M.S., F.R.C.S., F.R.C.O.G., Arthur C. H. Bell, M.B., B.S., F.R.C.S., F.R.C.O.G., Hon. M.M.S.A., Douglas MacLeod, M.S., F.R.C.P., F.R.C.S., F.R.C.O.G., W. R. Winterton, M.B., F.R.C.S., F.R.C.O.G., H. G. E. Arthure, M.D., F.R.C.S., M.R.C.O.G., Briant Evans, M.B., B.Ch., F.R.C.S., M.R.C.O.G., Kathleen M. Robinson, M.D., F.R.C.S., M.R.C.O.G., and S. G. Clayton, M.D., M.S., F.R.C.S., M.R.C.O.G.; Seventh Edition; 1948. London: J. and A. Churchill, Limited. 9" × 6", pp. 590, with illustrations, some of them coloured. Price: 28s.

GYNÆCOLOGICAL HISTOLOGY.

Too many medical text-books attempt to cover the needs of the undergraduate as well as of the post-graduate, of the general practitioner as well as of the specialist, and thereby become unsatisfactory to everyone. Josephine Barnes's "Gynæcological Histology", however, has been written with the definite purpose of providing a simple guide to the histology of the common gynæcological conditions.[1] It is therefore with considerable expectations that one begins its perusal, but the further one reads, the greater becomes the disappointment, and in the end one puts it away sadly.

The reasons for the failure of all the laudable intentions are manifold. First of all, there is perhaps no task so difficult as the attempt to condense in a page or two what occupies in the ordinary text-book a chapter of 20 or 30 pages, or to give a satisfactory description of a microscopic slide in three or four lines. To succeed in such a task one has to be not only an expert pathologist, but also a master of the written language. Secondly, the book has originated from annotations in a catalogue of a collection of microscope slides for the use of students. This becomes quite obvious as one notes the absence of descriptions and illustrations of a number of common and important conditions, while some quite rare lesions have received more than their due share of space. On many other occasions it is quite clear that the illustrations are photographs of slides that happened to be in the collection, but not of the best possible examples of the subject under discussion. Still, the illustrations are on the whole the best part of the book. The comments to them already suffer from many questionable and even inaccurate statements. The greatest shortcomings are actually found in the introductory pages to each chapter. While over-condensation is certainly responsible for some of the shortcomings, it is rather astonishing that chapters dealing with more uncommon and difficult conditions are on the whole quite well done, while, for example, those on the menstrual cycle and its disturbances, or on the placenta, are open to grave criticism. The classification of ovarian tumours presented by the author is quite impossible because of its disregard of basic principles. It is a pity that this book, of which the purpose and intentions deserve nothing but praise, cannot be recommended for the general use of students.

[1] "Gynæcological Histology", by Josephine Barnes, M.A., D.M. (Oxford), M.R.C.P. (London), F.R.C.S. (England), M.R.C.O.G.; 1948. London: Harvey and Blythe, Limited. 8¼" × 5", pp. 260, with many illustrations. Price: 30s.

The Medical Journal of Australia

SATURDAY, MAY 28, 1949.

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COLLAPSE THERAPY IN PULMONARY TUBERCULOSIS: A CONFUSED SUBJECT.

As the manner in which collapse therapy in pulmonary tuberculosis exerts its beneficial effects has never been quite settled, the methods of treatment embraced by this description have always been touched with a certain empiricism. Today no one would deny that collapse therapy is of help to very many patients, or even that in one form or another it is often necessary for the preservation of life; however, that empiricism is reflected in the general acknowledgement that some physicians are more radical and some more conservative than others in its use. It has lately been greatly emphasized by the result of a special study conducted in June, 1948, at the instigation of a committee of the American College of Chest Physicians, in which an attempt was made to determine the kind of treatment that is being used in the commonly seen, uncomplicated cases of pulmonary tuberculosis in the United States.[1]

The committee selected ten cases of pulmonary tuberculosis, representing problems seen regularly by any consultant in diseases of the chest: there were no "trick cases" nor unusual problems. Details of each case, together with copies of an X-ray film of the chest of each patient, were sent to fifty-nine highly experienced chest physicians. In respect of each of the ten patients the chest physicians were asked to answer the following questions:

1. Would you use collapse therapy for this patient?
2. If so, what kind?
3. When?
4. If collapse therapy is used, (*a*) how long would you continue it? (*b*) what would be your criteria for stopping it?
5. Is streptomycin indicated?
6. If so, (*a*) when? (*b*) in what dose? (*c*) for how long?
7. How long would you keep this patient in bed (*a*) before collapse therapy (if used)? (*b*) after?
8. Remarks?

The answers received indicated an astonishing divergence of views among the physicians consulted: in fact, they had with one or two exceptions no significant points of agreement. The chairman of the committee, Dr. Edward R. Levine, of Chicago, comments that the results of the survey cast considerable doubt on the value of any collected statistics on the efficacy of the various forms of collapse therapy. He points out that unless the indications for any given procedure are reasonably standardized and the management of this procedure during the course of the disease has likewise some uniformity, the end results bear no relationship to each other and are practically impossible to correlate. Had the cases selected been complicated ones, or had the physicians consulted been selected at random, so that their experience was a very variable quantity, it might not have been difficult to explain wide differences of opinion; but the cases without exception were simple and uncomplicated and of the type used for demonstration and teaching to students, while the physicians were all men of standing and of experience in collapse therapy. "It is customary", writes Dr. Levine, "for scientific men to base their judgement on clinical experience and statistical results of treated cases. Is it possible that similar cases have varied so markedly in the hands of different men, or is it possible that some physicians are using prejudice and impressions in place of information? There is, of course, the other possibility, and that is that uncomplicated tuberculosis does as well or as poorly, as the case may be, under any one of the recommended treatments." He concludes: "Up to this moment most of us believed that, although differences of opinion existed, fundamental principles of treatment were agreed upon by all. This study tells us how wrong we have been."

The American College of Chest Physicians decided to extend this study greatly during the year ending in June, 1949. No doubt, physicians everywhere who are charged with the responsibility of treating patients with pulmonary tuberculosis will find the results equally as interesting as those of the present survey, though it is to be hoped that some means will be found to bring the physicians whose opinions are to be sought into personal contact with the patients who are to be the subjects of the investigation. Indeed, it seems curious that fifty-seven out of fifty-nine experienced physicians should have been found willing to advise particular treatments for patients about whom they were as meagrely informed as in the recent study. The information circulated was superficial to a degree and comprised no details whatever of the patients' personality, temperament or background. This was a fault. Had these details been made available some of the "simple, uncomplicated" cases might have been found to present more than one highly complex problem. We cannot believe that the chest physicians of America in their own practice take so mechanistic a view of pulmonary tuberculosis that they are willing to treat the case and not the patient.

However, if this obvious source of fallacy is put to rights and the results of the current survey show the same or even greater divergence of thought and practice than the one lately completed, we need not feel alarm or despondency. Different ships, different longsplices. *Quot homines, tot sententiae: suus cuique mos.* It is no reproach that different chest physicians reach the same goal by different roads, and the totter-up of figures must be very careful how he criticizes. While the statistician shrinks in dismay from the numerous variables involved in this problem of the treatment of tuberculosis, the experienced clinician may integrate them all accurately by a scarcely conscious mental process. This is no idle

[1] *Diseases of the Chest*, November-December, 1948.

contention, but one which we have good reason to believe to be true. We have explored the subject on several occasions in these pages. In a leading article on November 2, 1940, we traced the history of "Empiricism in Medicine" and showed that it still finds and will continue to find a place in our practice. In another leading article on "Clinical Judgement *versus* Mathematical Proof" on January 15, 1944, we reached the conclusion that those very prejudices and impressions that Dr. Levine decries, when they are those of a trained observer, might well be worth more than the most carefully collated statistical material. Still, mathematics may give precision to our knowledge, and as yet there is room for humility in the practitioner of collapse therapy as he fingers his edged tools.

Current Comment.

PHYSIOLOGICAL CHILDBIRTH.

THE name of Grantly Dick Read and his teaching regarding physiological childbirth are well known, not only to the medical profession, but also to the general public. It will also be remembered that Mary de Garis has in the past written on several occasions in this journal on the subject. Read asserts that there is no physiological evidence that childbirth should be painful, or that pain can serve any useful purpose in labour. Pain in uncomplicated labour is due to fear, which is an artefact based on a wrong belief that pain is an essential accompaniment of childbirth. Fear, in Read's view, causes protective nervous discharges throughout the central nervous system, whose efferent impulses increase the tone of the muscle system they supply. In the uterus this causes resistant tension in the circular muscle fibres of the lower uterine segment. Resistance to the expulsing muscle produces excessive tension, which is recorded as pain by the uterine nociceptors. Working on this theory, Read instructs the women during pregnancy and labour "to remove fear and induce a state of mind which is understanding and serene, and a state of body which is physically fit and muscularly relaxed and controlled". In support of the practical value of his ideas Read has published[1] his results in the management of 516 consecutive labours at the Maternity Hospital, Woking. The group was probably one of more than average difficulty as many came to the hospital who had had previous difficulty in labour or who feared it so much that only the news about physiological childbirth had induced them to embark upon the process. They were given antenatal instruction in simple physical exercises—relaxation and respiration—and in the elementary phenomena of pregnancy and parturition. Labour was conducted with attention to the emotional as well as the physical changes that take place during normal childbirth. The main principles adopted were to avoid interference, pain and any horror of childbirth. The 516 labours ended in 429 physiological deliveries (83·2%), 52 forceps deliveries (10·1%), 28 Cæsarean sections (5·4%) and seven pairs of twins (1·3%). There were no maternal deaths and only one fœtal death, due to subtentorial hæmorrhage. The duration of all stages of labour was considerably shorter than the generally accepted average. In a majority of cases blood loss was minimal, a fact attributed by Read to four factors: (i) the consciousness of the mother; (ii) the fondling and sometimes suckling of the baby by the mother immediately the cord was severed; (iii) no interference with the uterus; (iv) expulsion of the placenta by the mother when the length of cord showed it to be in the vagina, and when uterine contractions were reestablished. No drug of any kind was given to 239 mothers (50%), 47 had chloral and bromide only and 23 had barbiturates only. When they were required, however, analgesics and anæsthetics were not withheld. Read points out the importance of sleep during the early hours of labour for the *primigravida* and favours the use of chloral and bromide. "A knowledgeable exhibition of sedatives in the first stage of labour in most cases obviates the desire or the necessity for analgesics or anæsthetics in the second stage." He considers that there are four "emotional menaces": the first when the cervix is about three-fifths dilated (a crucial stage requiring careful management); the second about the transition from the first to the second stage of labour, when "the ultimate and maximal dilatation of the cervix is referred to the lumbosacral region as backache" (an analgesic or sedative may be needed); the third when the advancing head meets the floor of the pelvis, the reaction being one of escapism, so that the patient needs explanation and encouragement; the fourth at the early crowning of the head, when nitrous oxide anæsthesia should be offered, though few women are said to accept it, and it is better for them to be allowed to witness the birth of the child; carbohydrate and fluids are desirable at the fourth "menace". In Read's series 375 mothers were classed as "good cooperators"; all watched the birth of the child, most of them held the infant's hand before its sex was known, and in all cases the baby, adequately wrapped, was given to the mother as soon as the cord had been severed. Some mothers put the baby to the breast at once, "with a salutary influence on uterine contractions and placental separation". Breast-feeding was encouraged and 98% of the babies were breast-fed when they left hospital. Throughout, the emphasis was on the physiological nature of the whole experience, though sedatives, analgesics and anæsthetics were given when they were required (never, however, against the wish of the woman) and forceps delivery or Cæsarean section was performed with appropriate indications. The important point is Read's statement:

> The outstanding impression gained from the women in this series is the absence of all aversion to parturition. They speak of the supreme happiness of childbirth. Their euphoria is without design. They desire to repeat the experience as soon as the economic and domestic difficulties of our present social disorganisation make possible the housing and upbringing of another child.

Read and his methods have their critics, and no doubt it is possible for him to overstate his case. It must also be remembered that some women who have had difficult first labours, have in subsequent deliveries experienced no difficulty and this without any treatment of the kind suggested by Read. However, whether or no his theory is correct, the results are impressive and demand the careful attention of all concerned.

[1] *The Lancet*, April 30, 1949.

FURTHER EXPERIENCES WITH "ANTABUSE".

A GOOD deal of interest has been evident in the results of Danish investigations into the effects of "Antabuse" and its possibilities as a treatment for alcoholism. We referred to reports by Hald and Jacobsen and by Martensen-Larsen in these columns on January 29, 1949. Now an account is available of its use in Canada with some new points of interest. R. G. Bell and H. Ward Smith[1] have tried the drug on themselves and have given it to nine patients. In their own case, they took 0·5 gramme of "Antabuse" daily for four days and then alcohol. The effects, which were observed by two professors of pharmacology and two psychiatrists, were similar to those already reported with some additions. In one case the peripheral vascular collapse was both subjectively and objectively much severer than was expected. In both cases the oral temperature fell to 97° F. No nausea or vomiting occurred. Recovery was delayed for five hours longer than was expected in one case, with severe throbbing headache and an inability to remain erect owing to a sensation of impending collapse; and three hours longer than expected in the other case. Among the patients it is to be noted that a number of mild symptoms, though no severe symptoms, were experienced and these were apparently due to

[1] *The Canadian Medical Association Journal*, March, 1949.

XUM

the "Antabuse" *per se*. The administration of alcohol to alcoholic patients produced the effects reported by the Danish workers with the following additional phenomena. One patient, a heavy whisky drinker, was given five ounces of whisky over a period of one hour, though he asked for more and would have drunk much more in the same time by normal habit. Ten minutes after, his breathing slowed and ceased altogether; it was reestablished with artificial respiration and oxygen, but remained slow for thirty minutes. Then he began to vomit. His venous blood alcohol concentration was 62 milligrammes *per centum*. Vomiting continued for four and a half hours. Next day he had a "hangover" worse than any ever experienced before and some of these had included *delirium tremens*. Another patient consumed beer at a much slower rate than normal and had only mild symptoms, though two ounces of whisky taken later caused severe symptoms, including vomiting. Yet another patient took 24 ounces of beer in five minutes and developed the full syndrome. A fourth patient developed severe migraine-like headaches persisting for twelve hours. An important fact illustrated by these experiments is the relation between severity of symptoms and rate of accumulation of alcohol in the blood. The danger is also pointed out of giving "Antabuse" to a patient with appreciable amounts of alcohol in his body. These persons may have blood alcohol concentrations of up to 400 milligrammes *per centum* and the results may be disastrous. There is as yet no means of controlling the severity of the reaction once established, though in one case oxygen appeared to give some benefit, and the drug must be used with care and full appreciation of its dangers. These Canadian workers endorse, however, the Danish opinion that "Antabuse" will prove valuable as an adjunct in the treatment of the alcoholic patient.

THE ARTERIAL SUPPLY TO THE FEMORAL HEAD.

THE arterial supply to the head of the femur provides a particularly good example of the clinical relevance of exact academic knowledge—in this case, accurate anatomical knowledge. Avascular necrosis of the femoral head is most often seen after fracture of the neck of the femur, but it may also be due to slipping of the upper femoral epiphysis, reduction of congenital dislocation of the hip joint and pyogenic or tuberculous infections of the femoral neck; it is also generally considered to be the pathological basis of Perthes's disease. In pointing out the importance of an accurate knowledge of the arterial supply to the femoral head in an understanding of these problems, F. R. Tucker[1] also draws attention to the contradictory views found in the voluminous literature on the subject. He sets out to clarify the position. After a review of the history of investigations in this field he describes his own research carried out in the department of orthopædic surgery in the University of Liverpool. His study is based on the examination of 44 femora obtained from fresh cadavers, the ages of the subjects varying from birth to seventy-seven years; 24 were children and 20 were adults. The arterial system was demonstrated by injection of radioopaque material, with Spalteholz's method of clarification, and histological section of the neck and *ligamentum teres*. Tucker states that the upper end of the femur is supplied by the nutrient artery of the shaft, the retinacular vessels of the capsule and the foveolar artery of the *ligamentum teres*. The retinacular vessels consist of three separate groups: postero-superior, postero-inferior and anterior. These vessels are the chief supply to the epiphysis and femoral head at all ages. The first two groups are branches of the medial femoral circumflex artery and they run along the upper and lower borders of the neck of the femur. If one looks at the head and neck of the right femur from the medial aspect, the postero-superior vessels are found between the eleven and two o'clock positions, and the postero-inferior vessels between the five and seven o'clock positions. Although the groups may extend on to the front of the neck, they are usually posterior. These two groups are moderately large and quite consistent, the postero-superior group being usually the larger, and occasionally providing the sole supply to the epiphysis. The anterior group is the smaller and less constant; its vessels are branches of the lateral femoral circumflex artery. The retinacular vessels lie loosely under the synovial membrane, sometimes in mesentery-like folds of the membrane. In their cervical course these vessels supply many branches to the femoral neck, which anastomose with the nutrient artery of the shaft. Branches from the superior vessels are particularly numerous and they run a remarkably straight path from their origin to the base of the femoral neck. Despite the attachment of these branches, the midcervical parts of the retinacular vessels are quite mobile, in marked contrast to the fixation which may be noted as they approach the articular cartilage. The postero-superior group of retinacular vessels do not pierce the epiphysial cartilage; they cross the plate at its periphery and then turn towards the centre of the femoral head. The postero-inferior and anterior vessels often cut the corner of the plate. Within the substance of the head, the retinacular vessels anastomose with each other, and with the nutrient and foveolar arteries if these are present. The foveolar artery constitutes a small and subsidiary blood supply to the femoral epiphysis. In this series, it penetrated the cartilaginous or osseous head in 33% of young specimens and 70% of adult specimens. The foveolar vessels increase in size with age.

Tucker then goes on to discuss the clinical significance of the arterial supply to the femoral head in various conditions. He believes that if injury is the cause of Perthes's disease, vulnerability of the epiphysis to infarction will be greatest when the blood supply is derived largely from the postero-superior vessels. In other words, multiple sources of vascular supply provide a safeguard to the nutrition of the femoral epiphysis, and, in contrast, concentration of the vascular supply to one group of vessels constitutes a potential danger. Tucker believes that the postero-superior group of vessels is susceptible to pressure from the acetabular lip and its labrum in positions of forced abduction and external rotation of the hip, and that it is individuals with this pattern of vascular supply who are most prone to Perthes's disease. He also inclines to believe that fragmentation of the epiphysis of the head of the femur after congenital dislocation of the hip joint is due to pressure on the retinacular vessels, which are trapped between femoral neck and acetabular margin when the hip is fixed in full abduction and external rotation. In *epiphyseolysis capitis femoris* avascular necrosis is not a frequent complication. According to Tucker, unless slipping is rapid or extensive, the retinacular vessels are not likely to be damaged because of the mobility of these vessels. In patients with fracture of the neck of the femur, the fracture shaft angle may be accepted, Tucker states, as an index of the degree of displacement and probably, therefore, as a guide to the likelihood of damage to the retinacular arteries. In the treatment of this fracture with a Smith-Petersen nail, he points out, the foveolar vessels are more prone to damage if the nail is near the fovea and with its tip flush with the articular cartilage. The risk of damage from a Smith-Petersen nail may perhaps be reduced if it is inserted eccentrically and if the foveolar area is avoided. In the majority of cases of traumatic dislocation of the hip the *ligamentum teres* must be ruptured, so that there can be no vascular supply to the femoral head from foveolar vessels. The incidence of avascular necrosis must depend first upon the frequency of damage to retinacular vessels, and then upon the incidence of anastomosis between these vessels and the nutrient arteries. In children no nutrient vessel was detected crossing the epiphysial line from the metaphysis to the epiphysis. In some adults, however, there was such anastomosis. Thus, avascular necrosis after traumatic dislocation of the hip joint, due to rupture of the retinacular vessels in cases in which there is no adequate anastomosis between these vessels and the nutrient artery, must be expected to occur more frequently in children than in adults. All these conclusions and details of his anatomical investigations Tucker has set out fully in a splendidly illustrated article. It warrants the study of all to whom these problems are important.

[1] *The Journal of Bone and Joint Surgery*, February, 1949.

Abstracts from Medical Literature.

OPHTHALMOLOGY.

Bacitracin and Ocular Infections.

JOHN G. BELLOWS AND CHESTER J. FARMER (*American Journal of Ophthalmology*, October, 1948) report the results of treatment with bacitracin in 43 cases of external ocular infection. In acute cases in which sensitivity tests showed the organism to be susceptible to small amounts of bacitracin, recovery was rapid. In two of three cases acute kerato-conjunctivitis responded well, in a third not at all. For chronic conjunctivitis the drug was no more effective than other available chemotherapeutic agents. The authors state that experimental infections of the cornea and vitreous humour produced by a sensitive strain of hæmolytic *Staphylococcus aureus* can be prevented by bacitracin. Prophylaxis is effective up to four hours for the cornea and up to twelve hours for the vitreous infection. Bacitracin will check vitreous humour infections if injected intravitreally, even forty-eight hours after the inoculation.

Invasion of the Optic Nerve by Retinoblastoma.

A. B. REESE (*Archives of Ophthalmology*, November, 1948) has studied the invasion of retinoblastoma into the optic nerve, comparing 119 cases which occurred between 1878 and 1929 and 116 cases which occurred between 1934 and 1947. In the old series the tumour had spread beyond the *lamina cribrosa* in one out of two eyes and in the more recent series in one out of four eyes. In the old series the optic nerve was severed at operation beyond the extension in only one out of five, while in the later series this was achieved in two out of three eyes. In the later series the length of optic nerve removed was greater than in the old. It was rare for the tumour to extend into the optic nerve beyond the *lamina cribrosa* for more than a few millimetres and extremely rare for it to extend as far as eight to ten millimetres. In 10% of cases the tumour extended out of the globe by way of the sclera, a finding which presupposes chorioidal invasion. Tumour invasion of the nerve begins in the base of the physiological or glaucomatous cup and around the central vessels. Invasion of the chorioid occurred in 25% of cases. The size of the tumour in the globe has no bearing on whether or not the tumour extends into the nerve. The tumour arises from the nuclear layers of the retina and has a certain affinity for invading nerve tissue with little tendency to invade fibrous tissue. In an analysis of fifteen cases of death from retinoblastoma, in 60% there were blood-borne metastases to bones, viscera and lymph nodes. In only nine of the fifteen cases had intracranial extension occurred via the optic nerve, and in seven of these there was generalized leptomeningeal involvement. The author maintains that intracranial extension is not the result of extension via the substance of the nerve, but that after it has progressed ten millimetres it then gains access to the subarachnoid space at the site where the central vessels leave the nerve. Thence it spreads rapidly throughout the subarachnoid spaces, not only of the involved nerve, but of the chiasma and elsewhere throughout the cranium. The author concludes from this investigation that there is no justification for the combined intracranial and orbital operation for retinoblastoma.

Hypopyon Ulcer Treated with Crystalline Penicillin in Adrenaline.

A. SORSBY AND J. UNGAR (*The British Journal of Ophthalmology*, December, 1948) have shown that six-hourly injections of 50,000 units of crystalline penicillin can safely and with advantage be replaced by doses of 500,000 units of crystalline penicillin in adrenaline at intervals of twenty-four hours. The authors report a series of cases in which varying-concentrations of crystalline penicillin in adrenaline were used at intervals which varied with the concentration of the solution. All cases had a favourable outcome. In two cases patients were treated by retrobulbar injection of penicillin in adrenaline and in one the response was good.

Miotic and Antiglaucomatous Activity of Tetraethyl Pyrophosphate.

W. MORTON GRANT (*Archives of Ophthalmology*, May, 1948) reports the ocular effects of a new anticholinesterase chemical, tetraethyl pyrophosphate. Tetraethyl pyrophosphate is a colourless, water-soluble and lipid-soluble, hygroscopic liquid of low volatility. It is the principal active ingredient of a more complex substance, commercial hexaethyl tetraphosphate, which, because of strong nicotine-like action, was used in Germany during the war as an insecticide, being substituted for natural nicotine. Both compounds are highly effective inhibitors of cholinesterase. The author used the drug in fifteen patients with glaucoma in concentration of 0·05% to 0·1% in peanut oil. He states that the drug appears to be most effective in patients who respond appreciably to standard miotic drugs, such as pilocarpine. Disadvantages of tetraethyl pyrophosphate are the symptoms of spasm of accommodation for near vision, dimness of vision and aching of the eyes, particularly with excessive doses. In certain eyes a rise in tension may be produced by tetraethyl pyrophosphate.

X-Ray Therapy for Retinal Diseases with New-Formed Blood Vessels (Eales's Disease: Retinitis Proliferans).

J. S. GUYTON AND A. B. REESE (*Archives of Ophthalmology*, October, 1948) present a preliminary report on the application of intensive X-ray therapy to the posterior ocular segment in a series of patients with ocular diseases characterized by retinal and vitreous hæmorrhages, with secondary fibrous tissue formation and with new-formed blood vessels extending into the vitreous. A total of 22 eyes in 14 patients were treated. The dosage was varied considerably. The first patients treated received 400*r* three times a week. In the original cases 8000*r* to 10,000*r* were given through the temporal portal and 5000*r* to 6000*r* through the nasal, but in later cases this was reduced to a total of 3500*r* to 6000*r* given only through the temporal portal. Of the patients treated, eight were classified as having typical Eales's disease, four atypical Eales's disease and two diabetic *retinitis proliferans*. The first and most striking effect of therapy was the diminution in new-formed vessels. The smaller vessels disappeared within four to eight weeks, even if the total dose was only 3500*r*. In six eyes which received 10,000*r* or more, even the largest new vessels completely disappeared from ophthalmoscopic visibility. Regression of fibrosis was not so marked as regression of vessels. Scanty fibrosis responded well to therapy of 10,000*r* and dense fibrosis was reduced only slightly or moderately. In the group of eight cases of typical Eales's disease there has been only one recurrent hæmorrhage. However, the cases have been followed for only a short period. In the group of four cases of atypical Eales's disease there has been a recurrent hæmorrhage in one case. In the two patients with diabetic *retinitis proliferans* fresh hæmorrhages have appeared.

Barriers and Aids to Fusion.

M. EYLES (*American Journal of Ophthalmology*, September, 1948) divides barriers to fusion into two classes, those which prevent development of fusion and those which cause its breakdown. The author lists them as follows. (i) Diopteric causes: (*a*) due to unequal unioçular images, for example, anisometropia, high astigmatism, and aniseikonia, and (*b*) refractive—hypermetropia or myopia. (ii) Anomalous retinal correspondence. The author claims to cure over 50% of these cases in four to twenty-four treatments given pre-operatively to patients under the age of twelve years; another 15% to 25% will obtain true retinal correspondence in the first weeks after operation provided pre-operative bimacular stimulation has been given. (iii) Amblyopia. Fusion should be stimulated and attained before operation while amblyopia is in the process of being cured. (iv) Suppression. (v) Neurogenic anomalies, such as nystagmus. (vi) Hyperphoria and hypertropia. A vertical deviation of over five dioptres is usually beyond the range of fusion. (vii) Loss of central fixation and false fixation. (viii) Deviation of the visual axes. The visual axes must be restored to approximate parallelism by operation, the previous anomalies being first corrected and a fusion ability initiated before the operative procedure is commenced.

Post-Operative Hypertropia.

R. G. SCOBEE (*American Journal of Ophthalmology*, November, 1948) discusses post-operative hypertropia. He states that it has been shown that raising the lateral rectus a distance equal to its own width produces eleven prism diopters of hypertropia. It is possible that a surgeon may erroneously reinsert one of the horizontal rectus muscles a millimetre or so too high in operating on these muscles, but it is almost beyond the realm of possibility that one could erroneously reinsert one a whole width or even half a width too high, and even if such erroneous reinsertion were made, the maximum resultant deviation would not be more than eleven prism dioptres. As the vertical deviations which appear after surgery on the horizontal rotators are frequently of an order greater than this eleven prism dioptres, they must have been present pre-operatively. From an analysis of the actions of the various extraocular muscles the following predictions are made. If a

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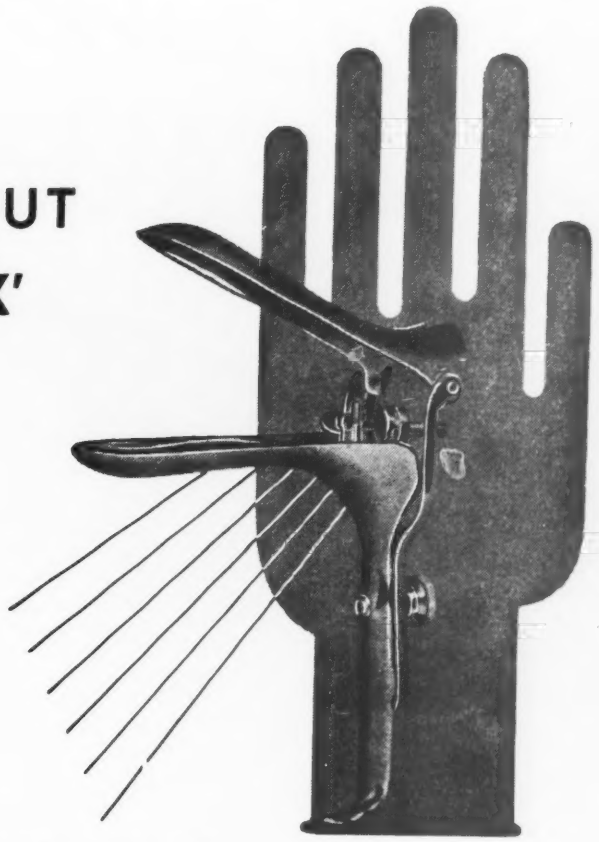

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vertical rectus is involved and there is esotropia, surgical correction of the esotropia will uncover or apparently exaggerate any existing vertical deviation. If a vertical rectus is involved and there is exotropia, surgical correction of the exotropia will cause any vertical deviation present to decrease or apparently disappear. If an oblique muscle is involved and there is esotropia, surgical correction of the esotropia will cause any vertical deviation present to decrease or disappear. If an oblique muscle is involved and there is exotropia, surgical correction of the exotropia will either uncover a vertical deviation or will apparently exaggerate any existing vertical deviation. These rules apply only to lateral heterotropia in which a single vertically acting muscle is involved.

OTO-RHINO-LARYNGOLOGY.

Fungous Disease of the External Auditory Canal.

JOHN J. CONLEY (*Archives of Otolaryngology*, June, 1948) states that an extensive historical review indicates that until 1937-1938 most investigators attributed inflammation of the external auditory canal to various microscopic fungi. Many articles were published dealing simply with clinical impressions of otomycosis. A large series of these organisms were considered to be pathogenic, *Aspergillus niger* and *Aspergillus fumigatus* being the commonest offenders. The most effective fungicides of clinical value were found to be salicylic acid 2% in alcohol, metacresylacetate ("Cresatin") and thymol. Observers from widely spread parts of the tropics, from 1937 onwards, repeatedly recorded the detection of pathogenic bacteria, chiefly *Bacillus pyocyaneus*, and only occasionally the fungi, so that it was concluded that the role played by fungi in infections of the external canal had been greatly exaggerated and that more emphasis should be given to pathogenic bacteria, particularly *Pseudomonas aeruginosa*. There has been a diversity of opinion about the part played by the wax in infections of the external canal. There has been some evidence of a bactericidal property, but to *Pseudomonas aeruginosa* this is not evident at all. The author has based the present paper upon the study of 32 cases in the Philippine Islands. The striking feature of the cultures was the predominance of *Pseudomonas aeruginosa* whether alone or along with other bacteria. Clinically and on culture this organism was found to manifest a great variety of colour development; black, brown, green, yellow and grey were noted. It was the organism which could most easily be mistaken for a fungus. Fungi occurred in only five cases and then in association with bacteria. The author states that geographic and seasonal relationships of diseases of the external auditory canal seem definite. In the tropics there is increased hyperkeratosis and maceration and the sweat and sebaceous glands are more active; these factors prepare the way for infection, which is resistant once established. In all the cases the patients were treated by aspiration of the debris with a fine suction tip. After cleansing, a wick soaked in 4% aluminium acetate solution was inserted into the canal and kept moist for two days. The process of cleansing was repeated as necessary, and when the condition was quiescent the canal was dusted with a fine sulphanilamide powder. The administration of one million units of penicillin daily for seven days was considered to have had no appreciable effect on the disease. For the cases in which fungi were demonstrated, packs of 1% thymol in metacresylacetate were applied.

The "Reverse King Operation" for Aphonia.

LEWIS F. MORRISON (*The Annals of Otology, Rhinology and Laryngology*, December, 1948) states that occasionally in unilateral vocal-cord paralysis the vocal cord remains fixed in extreme abduction, so that the patient is unable to develop compensatory action of the unparalysed cord sufficiently to produce a useful voice. To overcome this difficulty the arytænoid cartilage of the paralysed side is separated from its attachment and fixed in the mid-line. The approach is made through the side of the neck, as in the King operation for widening the glottis in laryngeal paralysis. The crico-arytænoid joint is exposed by cutting through the fibres of the crico-arytænoideus muscle and ligamentous capsule. In the author's case small fibrous bands were seen attaching the articular surfaces; these, too, were divided. A thin shaving of the articular surface is separated. Since it is observed that the upper rim of the cricoid cartilage is higher near the mid-line than the actual articular region, a small piece of approximately 1·5 millimetres is cut away in order to make certain that the transposed vocal cord shall remain on the same level as its fellow of the opposite side. The arytænoid cartilage is fixed in its new position with a single suture passed through the soft tissues of the posterior surface of the body of the arytænoid and thence through the posterior edge of the cut surface of the cricoid. The external wound is finally closed in layers in the usual manner. The effect in one case in which the author operated has been to restore the voice to good tone and useful volume while leaving an airway that is adequate in all respects. The author stresses that the operation was originally outlined to him by Brien T. King, originator of the operation devised for reposition of the vocal cords in cases of bilateral abductor paralysis.

Arytænoidectomy for Bilateral Abductor Paralysis.

DE GRAFF WOODMAN (*The Annals of Otology, Rhinology and Laryngology*, September, 1948) has devised a modification of the procedure of extralaryngeal arytænoidectomy of B. T. King. An incision is made along the anterior edge of the sterno-mastoid muscle for the length of the posterior border of the thyreoid cartilage. A vertical incision is then made along the posterior edge of the thyreoid cartilage through the perichondrium. The inferior constrictor is separated posteriorly, and while the cartilage is followed closely the perichondrium is separated around the posterior edge on to its mesial side. The facet-like joint between the inferior cornu and the cricoid cartilage is then separated. The incision is then carried through the perichondrium on the lateral wall of the cricoid cartilage and continued vertically upwards on to the arytænoid, so that the body is able to be dissected out subperichondrially. A traction suture of number 0 chromicized catgut is then placed submucosally around the vocal process, after which the remainder of the arytænoid cartilage is severed and discarded. The cord is then drawn laterally and fixed with the suture round the inferior thyreoid cornu or through a small hole bored in the adjacent cartilage. Closure is made by suturing the inferior constrictor muscle back into place and thence suturing the skin. A Penrose drain is left in the lower end of the wound for four days. The tracheotomy cannula is removed on the average after about twenty-eight days and should first be partly corked, so that the patient gains confidence in using the natural airway. Seven patients in the author's fourteen cases had improved voices. Five had only adequate voices. The average estimated size of the posterior glottic chink was 4·5 millimetres. A chink of over 6·0 millimetres may provide only a poor voice. An aperture of under 3·0 millimetres in one case provided an inadequate airway. In a further series of nine cases in which the method was employed by other surgeons, the voice was better in four, adequate in four and worse in one. In this last case the vocal inadequacy was due to too wide a glottic opening.

Radon Therapy of Naso-Pharyngeal Lymphoid Hypertrophy.

E. G. COLLINS, I. S. THOMSON AND G. E. SWINDELL (*The Journal of Laryngology and Otology*, January, 1949) review the results of treatment of lymphoid hypertrophies of 41 Aberdeen children. The treatment is considered to benefit two types of patient. The first is the child with catarrhal deafness. The second is the child suffering from chronic rhinitis which is often found to be associated with mucosal hypertrophy of the maxillary sinuses, as can be demonstrated radiographically. The applicator used carried 20 millicuries of radon in a platinum tube of 0·5 millimetre wall thickness and is regarded as delivering only γ radiations. Study was made of the likely surface dosage delivered and of the probable isodose at more distant points. It was considered that the applicator never lay nearer than 0·5 centimetre from the Eustachian cushion and thus that the dose delivered in one hour at that point was about 300*r*. At a depth of one centimetre in the tissues the dose decreased to 70*r* and at two centimetres to 30*r*. By comparison with an American applicator giving greater intensity of irradiation with less filtration and for very much shorter times, the comparative respective doses are calculated as 1520*r* at the surface, 55*r* at one centimetre and only 15*r* at two centimetres. In 11 cases of conduction deafness in which the treatment was used, resolution was achieved in six and improvement in three. In 24 cases of nasal catarrh, mucosal hypertrophy, which was evident in 22, was caused to regress in 18; resolution of symptoms occurred in 13 and improvement in seven. Where there was gross visible lymphoid hypertrophy in the naso-pharynx, shrinkage was not a noticeable effect, and it is considered that such evident hypertrophy should first be removed surgically. No harmful effects were produced by the irradiation therapy. The results obtained are considered superior to any achieved with antral lavage, nasal drops, vitamins or other treatment.

British Medical Association News.

SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on November 25, 1948, at the Robert H. Todd Assembly Hall, British Medical Association House, 135 Macquarie Street, Sydney, COLONEL A. M. MCINTOSH, the President, in the chair.

Investigation and Treatment of the Anæmias.

DR. RICHMOND JEREMY read a paper entitled "The Treatment of Anæmia" (see page 711).

DR. MARJORY LITTLE discussed the investigation of anæmia. She said that in the past the hæmatologist had been satisfied with an examination of the blood which included enumeration of the total red cells and white cells, estimation of the hæmoglobin content and examination of stained films; bone marrow received attention only in the post-mortem room. Even at the present time such a relatively simple examination might be sufficient for diagnosis in some cases, or at least supply useful information for diagnosis or treatment. With the introduction of methods for collecting bone marrow in the living subject, much fresh information concerning hæmatological problems had become available; but the procedure should be undertaken only after careful consideration, as it was not without discomfort and even risk to the patient. It should be carried out only when all other tests, including the observation of response to treatment, had failed to yield a diagnosis. If those standards were observed, cases of abnormal hæmatopoiesis in which examination of marrow was required would fall into a comparatively small group, of which the aleuchæmic leuchæmias and the so-called refractory anæmias comprised the majority. It was in helping to solve some of the problems of erythrocyte maturation and in the selection or observation of the effects of a particular therapeutic agent that the study of bone marrow obtained from the living subject had yielded the richest harvest. Marrow could be collected by puncture or trephine or both, and each method had its advantages and disadvantages. A counsel of perfection would suggest the use of both methods in every case; but puncture was the method of choice if only one was to be carried out. Material collected by puncture was always diluted with blood, so that the resulting picture was not that of marrow only; the marrow cells in smears obtained in that way were stained, as were the cells of the peripheral blood, and comparison of the one with the other could therefore be made. Material collected by trephine, on the other hand, was fixed, and sections were prepared; correlation of cells in such preparations with cells in films of the peripheral blood was difficult if not impossible. Fixed specimens, however, did present the architectural structure of the marrow rather than the separate marrow cells, and were more likely to yield diagnostic evidence in such conditions as metastatic carcinoma, Hodgkin's disease, tuberculosis and myelosclerosis. In the evaluation of assistance afforded to diagnosis by the examination of marrow, it had always to be remembered that the cellular structure of marrow was essentially patchy, and that only a millimetre might separate one cellular picture from a totally different neighbour. In any particular case, therefore, it would probably be wise to accept as diagnostic only major changes in the marrow picture.

Dr. Little then went on to consider advances made in the study of hæmatology during the past twenty years.

Hæmoglobin.

Reference was made to recommendations put forward by the Hæmoglobin Subcommittee of the Section of Pathology and Bacteriology of the Branch and accepted by the Section. The first of these was that the hæmoglobin value of the blood should be expressed only in grammes per 100 millilitres of blood, and that the practice of expressing it as a percentage should be discontinued. Dr. Little said that the reason for the recommendation was clear when it was realized that a number of different values had been arbitrarily selected as the equivalent of 100%. The objection of some clinicians to the abolition of the percentage method of recording hæmoglobin values was based on the desire to retain the colour index; but hæmatologists had gradually realized that the older method of estimating the colour index did not make allowance for variation of cell size, which was an important factor in altering the colour index. That had led to the elaboration of a system of values known as the "system of absolute values", calculated on observed figures, to replace the older index system based on arbitrary, fixed normals. If, however, the practice of recording the colour index as part of a blood examination was to be retained, at least during the transition period, the subcommittee recommended the following formula for its expression:

$$\frac{\text{grammes of hæmoglobin per 100 millilitres of blood}}{3 \times \text{red cell count in millions}}$$

To obtain the absolute values referred to, a known volume of uncoagulated blood was centrifuged in a graduated tube until the corpuscles were packed down to a constant volume. The volume of packed red cells was recorded as the number of millilitres of cells per 100 millilitres of blood. The most useful absolute values obtainable by those measures were the mean corpuscular volume, the mean corpuscular hæmoglobin concentration and the mean corpuscular hæmoglobin. The mean corpuscular volume was determined by dividing the volume of packed red blood cells expressed in millilitres per litre of blood by the total number of red cells expressed in millions per cubic millimetre; that gave the average volume of a single red cell expressed in cubic microns, the normal value being 78 to 94 cubic microns. The mean corpuscular hæmoglobin concentration was determined by dividing the hæmoglobin value expressed in grammes per 100 millilitres of blood by the volume of packed red cells expressed in millilitres per 100 millilitres of blood, and multiplying the result by 100 to obtain a percentage value; that value represented the actual hæmoglobin concentration in the blood, and was the true indicator of the presence or absence of iron deficiency. The normal value was between 32% and 38%. The mean corpuscular hæmoglobin was determined by dividing the hæmoglobin value in grammes per litre of blood by the total red cells expressed in millions per cubic millimetre of blood. That represented the average hæmoglobin content of a single red cell expressed in micromicrogrammes. The normal value was between 27 and 32 micromicrogrammes. Dr. Little said that a study of the absolute values of a sample of blood yielded a key to diagnosis and treatment in the majority of cases of anæmia. An increased mean corpuscular volume indicated the presence of macrocytosis, and suggested the need, as a rule, for liver therapy. A low mean corpuscular hæmoglobin concentration indicated that the red cells were unsaturated and in need of iron. Even if the mean corpuscular volume indicated the presence of macrocytosis and a need for liver therapy, the determination of the mean corpuscular hæmoglobin concentration was particularly important as a guide to treatment in cases of pernicious anæmia. If during treatment the mean corpuscular hæmoglobin concentration fell below the average normal level of 32%, iron should be given in addition to liver.

The Erythrocyte.

Dr. Little said that the study of bone marrow preparations had yielded information of great value in diagnosis and treatment, but that the picture of the maturation processes of the erythrocyte was unfortunately still obscured by a confusion of terms. Before the introduction of marrow puncture, most hæmatologists had accepted Sabin's views that maturation of the erythrocyte proceeded from hæmocytoblast to megaloblast to erythroblast to normoblast to reticulocyte and to normocyte. Sabin used the term "megaloblast" to describe the cell intermediate between the hæmocytoblast and the erythroblast, which was the pro-erythroblast of Ferrata. According to Sabin's view, in the absence of an adequate supply of the hæmatopoietic factor, an abnormal development of megaloblast to megalocyte occurred, which, when adequate supplies of liver were presented, returned to the megaloblast-normoblast cycle. With the study of bone marrow by puncture, ideas of the process of red cell development had altered. Many had come to believe that the megaloblast was always a pathological cell, incapable of developing into a normoblast, but developing directly from the pro-erythroblast to the megalocyte, when an adequate supply of hæmatopoietic factor was not available. Davidson and his fellow workers had shown, however, that a megaloblastic marrow might become changed into a normoblastic marrow within six hours of the administration of liver in cases of pernicious anæmia, and that, Dr. Little thought, must surely be accepted as evidence in support of the view that the megaloblast was only what Whitby and Britton described as a deficiency distortion of the normoblast. However, there was little difficulty in differentiating between megaloblastic and normoblastic marrow, and it was on such differentiation that diagnosis and treatment might depend.

Reticulocytosis.

Experimental work on liver therapy had created fresh interest in reticulocyte production, and estimations of the number of circulating reticulocytes had helped in the

appraisal of response to and the standardization of therapeutic substances. Minot and Castle suggested that the rate of blood production in normal individuals was probably regulated by oxygen tension in the bone marrow, and that once the red cell count was over 3,000,000 per cubic millimetre, the demand of the anæmia upon the bone marrow was not sufficient to cause delivery of reticulocytes into the blood-stream. That probably accounted for the absence of reticulocytes once the total red cell count was over 3,000,000 per cubic millimetre, when the progress of a patient with pernicious anæmia was being followed. In the standardization of therapeutic agents, the reticulocyte response was a more delicate test than the total red cell count. In the diagnosis of hæmolytic anæmia and of unsuspected obscure hæmorrhage also, reticulocyte counts might be of great value.

Leucocytes.

Knowledge concerning the maturation processes of the leucocytes had not been recently much added to. The diagnosis of leuchæmia with a typical blood picture was not difficult, but diagnosis might be doubtful in the aleuchæmic type and in conditions with a leuchæmoid blood picture. Examination of the marrow had to be resorted to before diagnosis could be established in a certain number of conditions, such as myelomatosis, myelosclerosis, neoplasms and tuberculosis. Since the introduction of marrow examination, many unsuspected cases of myelomatosis had been discovered. In the diagnosis of blood dyscrasias in children particular caution was necessary. Anæmia, leucopenia and thrombocytopenia in a child, even though no immature red or white cells were found, were suggestive of leuchæmia at an early stage. On the other hand, a considerable increase in the number of non-granular cells of children might be seen in such relatively benign conditions as infectious mononucleosis, whooping-cough and acute infectious lymphocytosis. Cases of infectious mononucleosis with the characteristic blood picture presented no difficulty in diagnosis; but according to Tidy, alterations in the types of white cells and their numbers took place so rapidly, and so great were the differences in different cases, that no single blood picture was exclusively typical of the disease. There might be a transient initial leucocytosis with up to 75% of polymorphonuclear cells, while leucopenia was fairly common at the onset. Tidy also discussed the value of the Paul and Bunnell test, and concluded that there was a question as to whether or not there were two types of infectious mononucleosis yielding respectively positive and negative results to the test. A positive result was proof of infectious mononucleosis; a negative result did not exclude it. In acute infectious lymphocytosis, the total leucocyte count might reach 100,000 per cubic millimetre, up to 90% of the cells being small lymphocytes; the absence of anæmia and the presence of many platelets should suggest the correct diagnosis. All cases of lymphadenopathy of any standing and many cases of splenomegaly demanded extensive laboratory investigation. Rich, in 1936, had referred to the importance of the lymphoid tissue, and lamented the complete ignorance of the function of the lymphocyte; but the conception that the lymphocytes were closely connected with protein metabolism and contained antibodies that could be released experimentally by appropriate stimuli in animals, had been generally accepted, and suggested that lymphocytes might be found to possess a value at present unrecognized.

Blood Platelets.

Dr. Little pointed out that enumeration of the blood platelets was an essential part of complete hæmatological examination, particularly of patients presenting features suggestive of a hæmorrhagic diathesis. Essential thrombocytopenia could be explained theoretically on a basis of bone marrow failure or depression of platelet production by reason of a splenic inhibitory factor, and it had been suggested that thrombocytopenic purpura in which megakaryocytic budding and hyperplasia could be demonstrated in marrow smears responded well to splenectomy, while failure to respond was associated with megakaryocytic hypoplasia; the application of that suggestion to surgical procedures, however, had not been as fortunate as was expected. Whitby in a recent paper had drawn attention to the significance of the presence of megakaryocytes or giant platelets in the circulation, and quoted Minot's opinion that their presence was an indication of a serious disturbance of bone marrow. The bone marrow disturbance was commonly leuchæmic in origin, but might be associated with the myeloid metaplasia frequently seen with myelofibrosis. If specimens of marrow were also found to contain an increased number of megakaryocytes, a diagnosis of myelofibrosis merited careful consideration.

Acholuric Jaundice.

Although some workers doubted the existence of an acquired type of acholuric jaundice, there was general agreement that prognosis was better in the congenital group. Discrimination between the acquired and congenital groups might be made by the application of the observations of Booman, Dodd and Lentil, who had noted that the washed red cells of patients with acquired hæmolytic jaundice were agglutinated by an anti-human-serum rabbit serum, while such serum had no effect on the washed red cells of patients with congenital hæmolytic jaundice.

Rh Factor.

Dr. Little said that consideration of the Rh factor was of primary importance from the diagnostic point of view in hæmolytic disease of the newly born, and discussed briefly the history of its discovery.

Conclusion.

In conclusion, Dr. Little said that failure of therapy to produce the expected response in any case of anæmia should suggest the possibility of associated thyreoid insufficiency, of impairment of renal or hepatic function, and most, important of all, of a mistaken hæmatological or clinical diagnosis. It had also to be remembered that the laboratory diagnosis of the anæmias was not limited to examination of the blood and bone marrow. Assistance was frequently obtained from examination of the fæces for occult blood, of gastric contents for free hydrochloric acid, of an excised lymph gland for histological structure, and of serum for protein and pigment content. It seemed not unlikely also that the application of histo-chemical methods to hæmatology would be utilized by biochemists in the near future to determine the chemical composition and functional activities of the cells in the blood and the marrow, and that that might lead hæmatologists into new and exciting fields.

DR. WILFRED EVANS said that both the speakers had given an admirable account of a difficult subject. It seemed to him that the anæmias could be divided into two classes, those which were clearly defined and adequately treated, and those which were not. Examples of the first type were pernicious anæmia, idiopathic hypochromic anæmia, acholuric jaundice and hæmorrhage. Of the second type normocytic hypochromic anæmia, mentioned by Dr. Jeremy, was an example. Dr. Little had said that in many such cases the anæmia followed chronic hæmorrhage, in some it was associated with thyreoid deficiency or with malignant disease, and in many it was due to chronic nephritis. In many cases it responded to no form of treatment; the patients were tried with folic acid, iron and liver, and they might respond temporarily to blood transfusion. They presented a great difficulty in practice. Dr. Evans went on to say that in the large group of acquired hæmolytic anæmias, some were due to the Rh factor in childhood. Yet in adults one commonly met with such anæmias, of which the ætiology was unknown and treatment was difficult. Some patients hæmolysed not only their own erythrocytes, but also those given in blood transfusions. An example of the difficulty that such patients caused had occurred within the preceding week at Sydney Hospital. The patient was suffering from acquired hæmolytic anæmia and was given a blood transfusion, and suddenly died. The post-mortem examination disclosed a large mass of agglutinated blood, which had been hæmolysed in the patient's system and had caused death. Such anæmias presented a great problem. It was not known whether the hæmolytic agent was in the spleen or in the blood-stream. Splenectomy was sometimes useful, but not always. Another large group included Felti's syndrome with arthritic symptoms, splenic anæmia, hypersplenism, and aplastic anæmia with leucopenia, thrombocytopenia, anæmia, and hyperplasia of the bone marrow. Dr. Evans said that there were two opposing theories in regard to the origin of those diseases: (i) that the spleen produced a hormone which prevented the maturation of the red blood cells in the bone marrow, and (ii) that the phagocytic action of the spleen was increased and the blood cells were destroyed too rapidly. In either case splenectomy was indicated. In some cases of splenic anæmia, as Dr. Jeremy had said, it was necessary to remove the spleen and also to anastomose the portal vein with the *vena cava*.

DR. A. H. TEBBUTT said that he had listened with great interest to the papers; both speakers had given a clear conception of modern ideas on the subject, both pathological and clinical. Dr. Tebbutt had hoped that the speakers would put forward some bizarre views to criticize; but they had not done so. There were many controversial points about the anæmias, but the speakers had expressed their own doubts about them. Dr. Tebbutt said that it seemed to him that they might soon arrive at the stage when the clinician would be able to prescribe specific chemical substances for

the macrocytic anæmias, just as he did for the hypochromic anæmias (iron *et cetera*). In that connexion folic acid was interesting, for it was a known chemical substance and had definite effects on the hæmatopoietic system in the macrocytic anæmias. Dr. Tebbutt went on to say that Dr. Jeremy had at first seemed to belittle the differences between crude and purified liver preparations. Dr. Tebbutt thought that it was agreed among clinicians that some anæmias refractory to purer preparations would respond to cruder preparations. That meant that there were some things in the crude preparations that were not in the others. He thought that Davidson had shown that proteolysed liver had hæmatopoietic effects in some macrocytic anæmias refractory to other liver extracts. He was glad that Dr. Evans had added something to what Dr. Jeremy had said about the splenic anæmias. He thought that the work of Dameshek and his co-workers was very interesting and stimulating. In splenomegaly with various combinations of cytopenias the physician would have to consider and investigate the part played by the spleen and perhaps revise and widen his indication for splenectomy. It was by no means clear how the inhibitory or humoral or hæmolytic effect of the spleen was exercised in some of the splenomegalies; but the splenic cytopenias were an interesting clinical and research field.

DR. K. T. HUGHES referred to sensitization to liver extracts in pernicious anæmia. He quoted a case that had occurred a number of years earlier. The patient was a woman suffering from classical pernicious anæmia, who was being treated with "Campolon" and later changed to "Anahæmin"; after several months she complained that twenty-four hours after each injection she did not feel well and had flushing of the skin. Larger doses were given without satisfactory response of the blood picture, and she still presented symptoms of sensitization. "Campolon" was substituted, and she responded without further symptoms. Another patient developed allergic symptoms during treatment with "Anahæmin"; treatment was continued, "Anahæmin" being given every second day for four doses with antihistamine substances given at the same time, without the development of further allergic symptoms, and the patient was able to carry on with her treatment satisfactorily without further recourse to antihistamine drugs. Up to the time of the meeting her blood count had been normal.

Dr. Little, in reply, said that she had nothing to add, except to thank those present for their favourable reception of her paper.

Dr. Jeremy, in reply to Dr. Tebbutt, who had referred to successful treatment of pernicious anæmia with crude liver extracts when purified extracts had failed, said that his own remarks had referred to classical pernicious anæmia and not to the other megaloblastic atypical forms of pernicious anæmia. Dr. Jeremy thought it interesting that very small quantities of substances like vitamn B_{12} would cure pernicious anæmia and its effects on the nervous system. He had been surprised to learn that tropical macrocytic anæmia and sprue responded to vitamin B_{12}; they had in the past responded to the crude liver preparations. Dr. Jeremy was interested to hear of Dr. Hughes's experiences with antihistaminic substances; he had not known that sensitization went along with a poor response to therapeutic substances. In conclusion, Dr. Jeremy thanked those present for their reception of his paper.

Colonel McIntosh, from the chair, thanked the two speakers for their interesting and instructive papers. He said that probably in no branch of medical practice was close collaboration between clinician and laboratory worker so essential as in the treatment of the various forms of anæmia. The speakers had given very interesting, very erudite and very up-to-date information about the various aspects of anæmia. Colonel McIntosh went on to say that it was gratifying that Dr. Little had maintained the active part in the meetings of the Branch that the women members had taken in recent days. He hoped that part would increase. It had undoubtedly had an elevating and stimulating effect on the meetings held.

Correspondence.

A NATIONAL MEDICAL SERVICE.

SIR: The letter from the three medical officers of the Northern Territory (May 7, 1949) puts one side of the question—the opposite scheme from the Government's view. It is a debatable point whether either represents the view of the informed majority in this country. However, there is a precedent which could be followed which would satisfy both sides if the Government were to put it into effect. That is the pre-war service of the Territory of New Guinea.

In the Territory every town of any size had a salaried government medical officer. He conducted public medical duties, sanitation, quarantine, police *et cetera*. He also conducted such private practice as he was asked to. Fees for this were paid or docked ("for professional attendance") to the collector of public moneys locally. The highest standard of medical ethics was customary. Statistics were kept, but no confidential information was allowed to leave the doctor's custody and no names were associated with the statistical reports.

If the town, as in the cases of Rabaul and Wau, were large enough to warrant it, private practitioners could set up. The public were free to consult whom they chose; the only difference was that they paid fees to the doctor instead of to the Government. Hospitals were open to both without differentiation.

This system could well be begun in Australia simply by recruiting medical men to the Health Department's service and placing them first in the towns which now can only support a doctor by means of a guarantee or some such scheme which practically amounts to a salary. In a few years' time the whole nation would have had a fair demonstration of the advantages and disadvantages of a national medical service, and its expansion or the reverse would then be the result of public opinion. No bitterness would remain.

Yours, etc.,
C. M. DELAND, M.B., B.S., D.P.H., D.T.M.

58 Park Terrace,
Parkside,
South Australia.
May 10, 1949.

CONSULTANTS AND GENERAL PRACTITIONERS.

SIR: "The old order changeth . . ." There was a time when consultants who were about to operate on patients sent to them by general practitioners made a point of informing the latter of the time and place of operation. Usually the referring practitioner was invited to be present and was asked if he would like to act as anæsthetist or assistant.

This courtesy seems to be unknown or at least to be disregarded by some of the newer generation of consultants. One may receive a letter stating the consultant's opinion and his intention to carry out certain procedures. One may hear no more until the patient calls to say he is now out of hospital after operation. Later, a letter may arrive from the consultant, announcing the result of the treatment.

Apart from any question of etiquette or intra-professional courtesy, the main point in bringing this matter up is that the referring practitioner, who will have to look after the patient later, is not afforded the opportunity of seeing what is done at operation.

Even admitting that a surgeon may prefer to have a selected anæsthetist and/or assistant, it seems important that the patient's own doctor should at least be invited to be present.

Yours, etc.,
A. BULTEAU.

7 Pittwater Road,
Gladesville,
New South Wales.
May 10, 1949.

BIOCHEMISTRY AND CANCER RESEARCH.

SIR: Cancer is a biological problem and cancer in the human subject is also a clinical problem, but ultimately newgrowth is related to altered chemical processes in the cell. Even if an extrinsic factor is found responsible, and any complete theory must take into account the so-called filterable tumours, the newgrowth process represents an orderly train of chemical processes differing from those of the somatic cell.

The orderly reactions of living matter are controlled by special molecules termed enzymes and also the hereditary factors or genes. Such molecules may be regarded as blueprints or templates, or they may be likened to the master disk of a gramophone record or to the organized set-up of type metal which prints a page of newspaper. The analogies may be pushed a little farther because there is reason to believe from optical activity that the mode of action is a surface one and the product of activity is a mirror image

of part of the master molecule. But there comes a time when the master molecule must be reproduced. From the persistence of inherited characters, it is obvious, in the case of the gene, that this is an exact and very reliable process. The two ways of splitting off new molecules represent the fundamental difference between the reproductive and vegetative activity of all living matter.

It is obvious that the gene must control the pattern of vegetative activity, but the routine work is usually delegated to a sort of substandard or enzyme, and in all but the most primitive forms of life the precious genes are enclosed in a protective nuclear membrane. In the actual mechanism of enzyme activity it is reasonable to suppose that the enzyme must come into contact or rather chemical union with the raw material or precursors of the substance to be formed. The precursors must become linked to the right part of a molecule, probably protein, which is of colossal size from the chemical viewpoint. The union may not be strictly chemical, for example, in a growing crystal of sodium chloride new units become attached to the mass in perfect order and alignment, or with a slight reduction in salt concentration, units will split off from a structure which surpasses in size any protein molecule. After the opposition of enzyme and precursor is effected energy must be added or subtracted. All chemical changes are accompanied by such energy changes, which may be expressed in heat units or in terms of the displacement of electrons in relation to the positive charges of the atomic nuclei. Energy used must be continually supplied, and in chlorophyll, a masterpiece of creation, the energy is supplied by two bands in the visible spectrum. Quite a lot is known of the oxidative enzymes of the animal cell, but it is difficult to understand how the energy produced is made available to the cell. In some reactions, of course, energy is lost as in the heat of muscle activity. The master molecule is able to deal with the energy necessary to transform the precursor until the new substance is split off and the process starts again. Most biological syntheses take place in several steps, and one might imagine the precursor somersaulting along a protein molecule with intermediate chemical changes at each point of contact. Vegetative activity does not follow a rigid formula. Primitive life readily changes its reactions to suit the environment, and in man the cells may be taught a new chemical process as when a child masters the toxin of measles.

The cancer problem is essentially a disorder of the reproductive activity of the controlling gene. However, knowledge of this process may well come from the study of the simpler reactions of the enzyme or even of the catalytic agent. Moreover, it might be possible to divert the reproductive activity of the cancer cell to vegetative processes. A histologist would call this differentiation. Cancer cells become differentiated, but to a varying and incomplete extent. It is no surprise that cancer of the prostate responds to œstrogens, because the architecture of the molecules must correspond in many respects with that of the normal prostate. Again the ability of tumour cells to utilize glucose anaerobically is only an inherited potential from normal cells. Probably the cancer change involves one or a limited number of genes which control the rate of cell reproduction. If the future proves the need for an extrinsic exciting agent, the same mechanism must function for the production of each new cell and the hypothetical virus must divide in step with the cell division. The trend of the argument is that there are many links in the cancer chain, most of them corresponding with the chain of activity of the normal cell. From the practical point of view there are probably many links where the chain of malignancy can be broken.

In order to search for vulnerable links material is necessary and uniform material is desirable so that varying results may be compared on a statistical basis. Transplantable tumours have been known for nearly half a century, but in spite of the vast amount of valuable work done, the path of research has not joined up with that of the clinician. On the other hand spontaneous human tumours when available have proved refractory to experimental investigations. Moreover, lack of uniformity prejudices such experimental work as can be carried out. On the other hand the study of hæmopoiesis with special reference to the leuchæmias appears to be a hopeful line of cancer research. It does not matter if the orthodox pathologist declares that leuchæmia is not a newgrowth. Here is a potential supply of fairly uniform cells produced by an anarchy of cell division. As a background there is the coexisting normal hæmopoiesis, a control guarding the most difficult provision of cancer research and treatment, that is, the simultaneous survival of normal cells.

Hæmatology gives some suggestions of possible differential action of curative agents. For example, numerous bacterial toxins, directly or indirectly, inhibit erythropoiesis with a coexisting granulocytosis. Sulphonamides on the other hand may inhibit granulopoiesis, while benzol first inhibits thrombopoiesis. The expert in allergy knows that cells can be readily taught to react in various ways to new antigens, and it is only another step to teach the cancer cell to absorb a curative substance. There is ample scope for choosing points of attack, and new research weapons are always becoming available. Organic radicals may be labelled by radioactive atoms while undergoing complex metabolic changes. New cytochemical methods are being developed to show premitotic reactions in the cell. The visible collection of genes called a chromosome, which takes such a spectacular part in mitosis, will not be discussed. This article is an attempt to present mainly well-known facts from a new viewpoint which may provide a better basis for an assault on the cancer problem.

Yours, etc.,

WARNFORD MOPPETT.

46 The Crescent,
Vaucluse,
New South Wales.

May 9, 1949.

THE ADRENALS IN RHEUMATISM.

SIR: Much comment has been raised in the last fortnight by reports in the lay Press of "Compound E", a substance discovered by Dr. Phillip Hench and Dr. Kendall of the Mayo Clinic. This is 17-hydroxy-11-desoxycortico sterone, which is an extract from the suprarenal cortex. It would appear from the personal investigations of one of the writers (L.J.A.P.) that this substance is of considerable value. It is being synthesized in America and will not be available for general use for at least eighteen months. This work on adrenal hormones is particularly interesting since adrenaline has been found to be of great value in cases of rheumatoid arthritis in our practice, particularly those with pyrexia that did not respond to sulphonamides, but which improved strikingly with the administration of adrenaline. As we previously reported in this journal, we have been experimenting for a number of years with sulphonamides in rheumatoid and infective arthritis. Owing to lack of success in some, or a stationary stage being reached in others or a relapse occurring, we employed adrenaline as additional therapy.

At first the dosage employed was 3 to 5 minims hypodermically of one in 1000 solution, twice daily, continued for months until the recovery occurred. We noted improvement in some very severe cases within a week and considered perseverance with the therapy as justified. With the wider use of "Proseptasine" therapy we temporarily abandoned the procedure, but recommenced in 1943 in cases which had resisted all therapy and especially where long-continued temperature and chronic illness had sapped vitality and destroyed resistance. We had in mind Douthwaite's report of cases of recovery following the administration of adrenaline. No other case, to our knowledge, has been reported in the literature. The hormone has acted beneficially in infective and true rheumatoid arthritis, but we prefer to use sulphonamides and calcium in addition.

It would seem that the adrenaline acts in the following way. It stimulates the splenic capsule to throw out lymphocytes and also stimulates the production of adrenal cortical hormone, which has been shown to produce dissolution of the lymphocytes in the tissues which results in the production of euglobulin. This substance contains γ globulin which is the main globulin in the blood from the immunological angle. Thus adrenaline promotes the production of immunity and in the chronic arthritic cases lack of immunity is so marked that it is an extremely valuable remedy.

Briefly to indicate its value. In a severe case of Still's disease in a child of fourteen with intermittent pyrexia for a year, in 1936, insulin, glucose and adrenaline were employed, the temperature falling to normal after one month of adrenaline therapy. Three minims, one in 1000 adrenaline, twice daily, was the dose employed. The child was well for a period of three years then relapsed. Subsequent therapy again restored her to health, but residual deformity remained.

The second case is that of a girl of sixteen years with persistent pyrexia for 14 months. Again adrenaline in conjunction with insulin and glucose produced recovery. After a period of health for three years she again relapsed, to pick up again with adrenaline therapy associated with sulphonamides and the intravenous administration of calcium.

In a severe debilitated case of ankylosing spondylitis (a male, aged twenty-eight years) with a high erythrocyte sedimentation rate of 42 and an eosinophile count of over 20%, reduction of the sedimentation rate to normal, quiescence of the active process and reduction of the eosinophile count to normal were established after adrenaline was given

twice daily for four months. A rapid change in his general condition was noted in seven days.

In three other cases, those of women completely invalided by rheumatoid arthritis, sulphonamides, insulin and glucose therapy were only of slight benefit whereas adrenaline proved over the last twelve months to be the remedy leading to subsequent recovery.

As vitamin *C* is concentrated in the cortex and is thought to be incorporated in the molecule of the cortical hormone, its importance in rheumatoid arthritis stressed by many writers becomes easily apparent. Our experience with patients bears this out.

The common occurrences of an overacting sympathetic in rheumatoid arthritis seemed to contradict the usage of a sympathetic stimulant like adrenaline, but this action is only a temporary one, the more important being its indirect promotion of γ globulin.

To summarize. In rheumatoid arthritis injections of adrenaline have been found to be of very great value, the substance in oil is injected twice daily in doses of 0·5 millilitre, the dose being later reduced to once daily.

Cases of rheumatoid arthritis with allergic basis or without it are responsive to therapy. Only in cases previous to the war was adrenaline employed alone. We prefer that the therapy should be additional to and should not replace the sulphonamides.

We are continuing to carry out clinical and laboratory investigations in this matter in the hope that further light may be shed on the rheumatoid arthritic problem, via the adrenal gland.

Yours etc.,

L. J. A. PARR,
PAUL WHITE.

135 Macquarie Street,
Sydney,
May 20, 1949.

HEREDITARY HÆMORRHAGIC TELANGIECTASIA ASSOCIATED WITH ELLIPTOCYTOSIS (OVALOCYTOSIS).

SIR: The combination of hereditary hæmorrhagic telangiectasia with elliptocytosis of the red corpuscles has been described by Penfold and Lipscombe[1] in a Jewish family in London. So far theirs is the only observation to be found in the literature.

The case here reported is as follows. A female, aged forty-two years, unmarried, with no siblings, came under observation while having a routine blood count prior to a surgical operation. Elliptocytosis of the red corpuscles was noticed while the red corpuscles were being counted in the counting chamber and on the dried films 84% of the corpuscles were elliptocytes (ovalocytes). The white cells were normal and there was no evidence of anæmia or of excessive hæmolysis. The blood belonged to group B and was Rh negative.

Telangiectases were clearly visible on the face, neck and sternum; none could be found on the mucous membranes. On my questioning the patient, she said the "blood spots" had always been present, but were becoming worse. There was no history of bleeding and no other developmental defects were found on examination. The family history was obtained in as great detail as possible. Both the patient's father and paternal grandmother had suffered from a similar condition of the skin, but at no time had either had a blood examination. Both died years ago. The blood of the patient's mother did not show any abnormality, but was the same blood group as the patient. None of the mother's relatives had ever shown any skin lesion.

Both elliptocytosis and multiple hereditary telangiectasia are mesoblastic defects and are inherited as Mendelian dominants.[2] Terry, Hollingsworth and Eugenio[3] regard elliptocytosis as an atavistic mutation which might furnish a link with the marine vertebrates, and Penfold and Lipscombe[1] put forward the interesting hypothesis that multiple hereditary telangiectasia is also a reference back to the amphibian state in which the mucous membranes of mouth and throat and also the skin are accessory breathing surfaces and therefore highly vascular. The gene for telangiectasis is not very uncommon and if every case which came under observation was examined for elliptocytosis of the red corpuscles some interesting data might be obtained; conversely patients with elliptocytosis should be carefully examined for signs of errors of development in the blood vascular system.

Yours etc,

EVA A. SHIPTON.

13 Macquarie Street,
Sydney,
January 29, 1949.

REFERENCES.

(1) J. B. Penfold and J. M. Lipscombe: "Elliptocytosis in Man Associated with Hereditary Hæmorrhagic Telangiectasia", *The Quarterly Journal of Medicine*, Volume XII (New Series), 1943, page 157.

(2) R. R. Gates: "Human Genetics", Volume 1, pages 615 and 627.

(3) M. C. Terry, E. W. Hollingsworth and V. Eugenio: "Elliptical Human Erythrocytes", *Archives of Pathology*, Volume XIII, 1932, page 193.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Numbers 33 and 34, of May 12 and 19, 1949.

AUSTRALIAN MILITARY FORCES.

Interim Army.

Royal Australian Army Medical Corps.

WX10 Lieutenant-Colonel (Temporary Colonel) J. H. Stubbe, E.D., is removed from a Regimental Supernumerary List and is transferred to Royal Australian Army Medical Corps (Medical) Citizen Military Forces, 5th Military District, 21st January, 1949.

VX700090 Captain R. W. Klein is appointed from the Reserve of Officers, 14th February, 1949.

V3581 Lieutenant-Colonel S. T. Appleford is placed upon the Retired List (3rd Military District) with permission to retain his rank and wear the prescribed uniform, 6th January, 1949.

NX506207 Captain (Temporary Major) P. A. McReady relinquishes the temporary rank of Major and is transferred to the Reserve of Officers (Royal Australian Army Medical Corps) (2nd Military District), 2nd March, 1949.

The following officers are transferred to the Reserve of Officers (Royal Australian Army Medical Corps) (3rd Military District).—Captains VX700029 B. Goldman, 2nd March, 1949, and VX700079 D. H. Harris, 4th March, 1949.

Citizen Military Forces.

Northern Command: First Military District.

Royal Australian Army Medical Corps.—1/39011 Captain (provisionally) J. H. Hood is transferred to the Reserve of Officers (Royal Australian Army Medical Corps) (1st Military District) with the honorary rank of Captain, 1st February, 1949.

Eastern Command: Second Military District.

Royal Australian Army Medical Corps. — 2/146528 Lieutenant-Colonel E. J. C. Molesworth, M.C., is appointed from the Reserve of Officers, with regimental seniority in accordance with Army seniority, and is borne supernumerary to the authorized establishment of Lieutenant-Colonels with pay and allowances of Major (at his own request), 1st April, 1948. Majors 2/50012 R. R. Winton and 2/50013 T. M. Clouston are appointed from the Reserve of Officers, with regimental seniority in accordance with Army seniority, 1st May, 1948. The following officers are appointed from the Reserve of Officers, with regimental seniority in accordance with Army seniority, 1st May, 1948: 2/126997 Major G. V. Mutton and Captains 2/79012 G. Clifton-Smith, 2/135669 L. W. Middleton and 2/126998 R. I. Eakin.

Southern Command: Third Military District.

Royal Australian Army Medical Corps.—3/50018 Colonel (Honorary Brigadier) H. G. Furnell, C.B.E., D.S.O., E.D., from Deputy Director of Medical Services, Headquarters Southern Command (Part-Time Duty), is appointed Deputy Director of Medical Services, Headquarters Southern Command, 1st July, 1948. 3/50053 Colonel J. G. Hayden, C.B.E., E.D., is appointed from the Reserve of Officers with regimental seniority in accordance with Army seniority, 2nd February, 1948, and is appointed Consultant Physician, Directorate of Medical Services, A Branch, Army Headquarters, 1st November, 1948. 3/50054 Lieutenant-Colonel (Honorary Colonel) E. V. Keogh, D.C.M., M.M., is appointed from the Reserve of Officers with regimental seniority in accordance with Army seniority, 1st April, 1948, relinquishes the honorary rank of Colonel, is appointed Director of Hygiene and Pathology, Directorate of Medical Services, A Branch, Army Headquarters, and is promoted to the tem-

porary rank of Colonel, 1st November, 1948. 3/50055 Major (Honorary Lieutenant-Colonel) R. Officer is appointed from the Reserve of Officers with regimental seniority in accordance with Army Seniority, 1st May, 1948, relinquishes the honorary rank of Lieutenant-Colonel, is appointed Consultant Surgeon, Directorate of Medical Services, A Branch, Army Headquarters, and is promoted to the temporary rank of Colonel, 1st November, 1948. 3/129123 Lieutenant-Colonel R. S. Smibert, O.B.E., is appointed from the Reserve of Officers with regimental seniority in accordance with Army seniority, and is borne supernumerary to the authorized establishment of Lieutenant-Colonels with pay and allowances of Captain (at his own request), 1st April, 1948. The following officers are transferred to the Reserve of Officers (Royal Australian Army Medical Corps) (3rd Military District): 3/101022 Major P. J. Parsons, 21st June, 1948, and 3/72793 Captain I. A. N. McCallum, 28th January, 1949.

Southern Command: Fourth Military District.

Royal Australian Army Medical Corps.—4/31907 Captain R. A. Burston is seconded whilst undergoing post-graduate studies in the United Kingdom, 27th October, 1948.

Southern Command: Sixth Military District.

Royal Australian Army Medical Corps: To be Captains (provisionally), 9th November, 1948.—6/15316 Donald Edmund Anderson, 6/9022 John Oliver and 6/15206 David John Walters (in lieu of the notification respecting these officers which appeared in Executive Minute No. 20 of 1949, promulgated in *Commonwealth Gazette*, No. 19, of 1949).

Western Command: Fifth Military District.

Royal Australian Army Medical Corps. — 5/32043 Lieutenant-Colonel (Temporary Colonel) L. E. Le Souef, E.D., from Deputy Director of Medical Services, Headquarters, Western Command (Part-Time Duty) is appointed Deputy Director of Medical Services, Headquarters, Western Command, 1st July, 1948. 5/32054 Lieutenant-Colonel (Temporary Colonel) J. H. Stubbe, E.D., is appointed from the Interim Army with regimental seniority in accordance with Army seniority, and is appointed Deputy Director of Medical Services, Headquarters, Western Command, 21st January, 1949. 5/32053 Lieutenant-Colonel (Honorary Colonel) F. K. Wallace, O.B.E., is appointed from the Reserve of Officers with regimental seniority in accordance with Army seniority, and is borne supernumerary to the authorized establishment of Lieutenant-Colonels with pay and allowances of Captain (at his own request), 1st April, 1948. 5/32043 Lieutenant-Colonel (Temporary Colonel) L. E. Le Souef, E.D., relinquishes the appointment of Deputy Director of Medical Services, Headquarters, Western Command, the temporary rank of Colonel, and is transferred to the Reserve of Officers (Royal Australian Army Medical Corps) (5th Military District), 21st January, 1949.

Reserve Citizen Military Forces.

Royal Australian Army Medical Corps.

2nd Military District.—The following officers are retired at their own request: Captain E. H. V. Lloyd-Williams, Honorary Captain C. J. Downes, 5th November, 1948.

3rd Military District.—The following officers are placed upon the Retired List (3rd Military District) with permission to retain their rank and wear the prescribed uniform: Honorary Brigadier W. W. S. Johnston, C.B.E., D.S.O., M.C., E.D., Colonels R. Fowler, O.B.E., V.D., A. F. Jolley and E. R. White, V.D., Honorary Colonel Sir H. A. S. Newton, Lieutenant-Colonel W. G. D. Upjohn, O.B.E., Honorary Lieutenant-Colonels A. J. Brenan and H. F. Maudsley, M.C., Majors K. M. Doig, M.C., J. V. H. Guest, J. T. Tait, F. T. Wheatland and N. R. Williams, O.B.E., 13th January, 1948, Major H. Shannon, 14th October, 1948, Honorary Majors C. Friend, E. M. Gordon-Glassford, M.C., H. R. Hyett, M. H. O'Sullivan, H. C. Trumble, M.C., and B. R. Woods, Captains F. E. R. Biggs, T. M. Hendry, R. G. Stott, S. G. Sutton, M.B.E., H. Symonds, T. J. K. Whittam and J. W. Young, Honorary Captain R. O. Mills, 13th January, 1948.

ROYAL AUSTRALIAN AIR FORCE.

Citizen Air Force: Medical Branch.

The appointment of Temporary Squadron Leader A. C. Newell (257690) is terminated on demobilization, 28th March, 1949.

Reserve: Medical Branch.

The appointment of Temporary Wing Commander G. B. Baldwin (251657) is terminated, 1st April, 1949.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

WEEK-END COURSE AT BROKEN HILL.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that a week-end course will be held in conjunction with the Broken Hill Medical Association at the Broken Hill District Hospital on Saturday and Sunday, June 11 and 12, 1949. The programme is as follows:

Saturday, June 11.—2.30 p.m., "Surgery of Peptic Ulcer", Dr. Norman Wyndham; 4 p.m., "Review of Cardiology", Dr. T. M. Greenaway.

Sunday, June 12.—10 a.m., "Breech Delivery", Dr. W. D. Cunningham; 11.30 a.m., "Repair of Difficult Herniæ", Dr. Norman Wyndham; 2.30 p.m., "Some Problems in Thoracic Diseases", Dr. T. M. Greenaway; 4 p.m., "Toxæmias of Pregnancy", Dr. W. D. Cunningham.

The fee for attendance is £2 2s., and those wishing to enrol are requested to notify Dr. J. T. Cullen, Honorary Secretary, Broken Hill Medical Association, Broken Hill, as soon as possible.

The Royal Australasian College of Physicians.

EXAMINATION FOR MEMBERSHIP.

AN examination for membership of the Royal Australasian College of Physicians will take place in October-November, 1949. The written examination will be held in capital cities of the Commonwealth where candidates are offering. The clinical examination will be held in Melbourne. Only those candidates whose answers in the written examination have attained a standard satisfactory to the Board of Censors will be allowed to proceed to the clinical examination.

Dates of Examination.

The dates of the examination will be:

The written examination will be held on Saturday, October 8, 1949, and the clinical examination in the week commencing November 7, 1949.

Application.

Applications to appear before the Board of Censors should be made in the prescribed form and must be in the hands of the Honorary Secretary of the College not later than Saturday, September 10, 1949. Candidates should signify in which city they desire to take the written examination. Application forms are obtainable from the Honorary Secretary, 145 Macquarie Street, Sydney.

Obituary.

CHARLES ALISTER McHARDY.

WE are indebted to Dr. Luxford Meagher, of Melbourne, for the following account of the late Dr. Charles Alister McHardy.

Inspired by personal rather than professional associations, I pen a few lines to the memory of my friend, the late Dr. Charles Alister McHardy, who died at his home at Double Bay, Sydney, on March 11, 1949, after a brief illness. He was born in Goulburn, New South Wales, forty-seven years ago and received his early education from the Marist Brothers at Newcastle. He graduated from the University of Sydney in 1926, and the following six years he spent in various hospitals and other spheres of professional work. In 1932 he began practice at Double Bay. From 1940 to 1944 he served with the air force as a squadron leader, and late in 1944 he resumed his practice at Double Bay.

We were friends for thirteen years, and throughout the whole of that time he proved himself loyal, sympathetic and kind. It was a period marked for me by a long illness, and he was indefatigable in his visits and his unfailing cheerfulness and good humour went far to reconcile me to the tedium of my state. His was the understanding heart:

his the bright mind of the perfect comrade. The cast of his mind was scholarly, and chivalry was one of the outstanding marks of his splendid character. In a letter to me of a recent date he clearly revealed that his mind was constantly occupied with the contemplation of the eternal verities. Alister McHardy was a practical Christian. Death surely found him well prepared.

MAVIS VICTORIA ZANE.

WE regret to announce the death of Dr. Mavis Victoria Zane, which occurred in London, England, on February 7, 1949. Dr. Zane, who before her marriage was Dr. Mavis Grant, graduated from the University of Sydney in 1918. After spending ten years as medical officer for girls' schools under the Egyptian Ministry of Education, she served in a number of English hospitals and child welfare clinics. She joined the staff of the Save the Children Fund in January, 1948, and was appointed medical superintendent of a hospital of 100 beds on the Baltic Sea coast at Schlutup, near Lubeck. Dr. Zane held this position until the hospital was transferred to the German authorities towards the end of the year. She was ill when she returned to England.

WILLIAM LOCKYER POTTER.

WE regret to announce the death of Dr. William Lockyer Potter, which occurred on May 9, 1949, at Port Melbourne, Victoria.

PATRICK FRANCIS VINCENT CROWE.

WE regret to announce the death of Dr. Patrick Francis Vincent Crowe, which occurred on May 13, 1949, at Goodna, Queensland.

ALBERT LESLIE STAFFORD.

WE regret to announce the death of Dr. Albert Leslie Stafford, which occurred on May 15 at Fairfield, New South Wales.

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Chauncy, James Hornridge, M.R.C.S. (England), L.R.C.P. (London) 1904, Burrinjuck Dam, via Bowning.

The undermentioned have been elected as members of the New South Wales Branch of the British Medical Association:

Endelman, Bogumil, registered under Section 17, Paragraph 2, of the *Medical Practitioners Act*, Flat 4, 84 Drumalbyn Road, Bellevue Hill.

Foldes, Aladar, registered under Section 17, Paragraph 2, of the *Medical Practitioners Act*, 28 Morrice Street, Lane Cove.

Price, Henty Michael, M.B., B.S., 1948 (Univ. Queensland), c.o. Mrs. R. Price, 6 Ithaca Flats, Ithaca Road, Elizabeth Bay.

Australian Medical Board Proceedings.

NEW SOUTH WALES.

THE undermentioned have been registered, pursuant to the provisions of the *Medical Practitioners Act*, 1938-1939, of New South Wales, as duly qualified medical practitioners:

Bennett, John Barkly, M.B., B.S., 1947 (Univ. Adelaide), c.o. Watson Victor Limited, 9 Bligh Street, Sydney.

Bretherton, Kenneth Wilbur, M.B., B.S., 1942 (Univ. Melbourne), 219 Miller Street, North Sydney.

The following additional qualifications have been registered:

Belisario, John Colquhoun, 143 Macquarie Street, Sydney (M.B., Ch.M., 1926, Univ. Sydney), D.D.M., 1947 (Univ. Sydney).

Bolliger, Walter, 300 Sailor's Bay Road, Northbridge (M.B., B.S., 1945, D.P.H., 1947, Univ. Sydney), D.T.M. and H., 1949 (Univ. Liverpool).

Elliot-Smith, Mervyn Harrie, 2 Mandalong Road, Mosman (M.B., Ch.M., 1923, Univ. Sydney), F.R.C.S., 1925, F.R.A.C.S., D.R.C.O.G., 1935 (Univ. Edinburgh).

Diary for the Month.

JUNE 1.—Victorian Branch, B.M.A.: Branch Meeting.
JUNE 1.—Western Australian Branch, B.M.A.: Council Meeting.
JUNE 1.—South Australian Branch, B.M.A.: Council Meeting.
JUNE 2.—New South Wales Branch, B.M.A.: Special Groups Committee.
JUNE 2.—South Australian Branch, B.M.A.: E. C. Stirling Lecture.
JUNE 3.—Queensland Branch, B.M.A.: Branch Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135 Macquarie Street, Sydney): Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

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